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UNIVERSITY OF SOUTHAMPTON

FACULTY OF MEDICINE

Academic Unit of Primary Care, Population Sciences and Medical Education

Volume I of I

Prevention and detection of liver disease in the general population

by

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Thesis for the degree of Doctor of Medicine

April 2020

UNIVERSITY OF SOUTHAMPTON

ABSTRACT

FACULTY OF MEDICINE

Public Health

Thesis for the degree of Doctor of Medicine

Prevention and detection of chronic liver disease in the general population of the UK

Kate Anne Glyn-Owen

Liver disease is the third biggest cause of premature death in the UK, yet two of its main causes - alcohol consumption and obesity – are modifiable risk factors, potentially amenable to public health prevention interventions. Chronic liver disease is generally progressive, usually starting with mild fibrosis and continuing through to cirrhosis. Signs and symptoms often do not appear until disease is at an advanced stage. As a result, many patients present late to healthcare services and outcomes are poor. Consequently, this work focused on the general population of the UK, where prevention strategies would best be targeted. The aim is to better understand the epidemiology of those at risk of liver disease due to obesity and alcohol consumption, and how disease may be identified early in its course, in order to improve patient outcomes.

To address this, large datasets from general population settings were analysed. This included conducting a meta-analysis of cohort studies, and analyses of national survey datasets. This thesis describes the distribution and overlap of alcohol and obesity risk factors for liver disease; risk of liver disease associated with individual risk factors and their combinations; distribution of non-invasive markers of liver disease; associations between non-invasive markers of liver disease and risk factors; and associations between overweight /obesity and calories from alcohol.

Key findings were that the majority of the UK general population have at least one risk factor for liver disease and nearly 30% have multiple risk factors. Awareness of the risk factors for liver disease in the general population was very low (4%). There was a significantly increased risk of liver disease associated with the combination of drinking above recommended alcohol consumption guidelines and being overweight or obese (OR 3.60 (95%CI 3.22 to 4.02) for overweight, OR 5·84 (95%CI 5·09 to 6·70) for obese). Some 12% of the general population had a

combination of increased alcohol consumption and increased BMI. We suggest the term 'BAFLD to describe these people at risk of **B**oth **A**lcohol and **F**atty **L**iver **D**isease. Non-invasive markers of liver disease showed significant variation in positivity in the general population setting, they were not concordant and their performance differed significantly between risk factor categories. Abnormal liver blood tests were found in 11% of the population. Calorie consumption was higher in those who consumed alcohol, and alcohol calories were consumed in addition to usual calorie intake. Weekly calorific intake from alcoholic beverages increased significantly with increasing BMI. Mean extra calories on days when participants consumed alcohol were 428 kcal (95%CI 396 to 460).

The data presented here further our knowledge of who is at risk of liver disease; the interplay of risk factors; the use of non-invasive markers in a general population setting; and the contribution of calories from alcohol in those with existing risk from increased BMI. It is hoped this evidence will inform risk stratification protocols, clinical pathways, prevention strategies and public health policy, in order to improve prevention and detection of chronic liver disease in the UK population.

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DECLARATION OF AUTHORSHIP

I, Kate Anne Glyn-Owen declare that this thesis and the work presented in it are my own and has been generated by me as the result of my own original research.

Prevention and detection of liver disease in the general population

I confirm that:

1. This work was done wholly or mainly while in candidature for a research degree at this University;
2. Where any part of this thesis has previously been submitted for a degree or any other qualification at this University or any other institution, this has been clearly stated;
3. Where I have consulted the published work of others, this is always clearly attributed;
4. Where I have quoted from the work of others, the source is always given. With the exception of such quotations, this thesis is entirely my own work;
5. I have acknowledged all main sources of help;
6. Where the thesis is based on work done by myself jointly with others, I have made clear exactly what was done by others and what I have contributed myself;
7. Parts of this work have been published as:

Papers accepted for publication in peer-reviewed journals

Glyn-Owen K, Böhning D, Parkes J, Roderick P, Buchanan R. The combined effect of alcohol and body mass index on risk of chronic liver disease: systematic review and meta-analysis of cohort studies. Accepted for publication in *Liver International* on 1.12.2020.

Conference oral presentations

Glyn-Owen K, Hounkpatin H, Ziauddeen N, Parkes J, Roderick P. A beer on the lips, an inch on the hips: alcohol calories and obesity in the National Diet and Nutrition Survey. Public Health England Public Health Research and Science Conference, Warwick, UK, March 2018.

Glyn-Owen K, Hounkpatin H, Ziauddeen N, Parkes J, Roderick P. Alcohol calories and obesity in the National Diet and Nutrition Survey. Wessex Public Health Conference, Southampton, UK, March 2018.

Glyn-Owen K, Hounkpatin H, Ziauddeen N, Parkes J, Roderick P. Alcohol calories and obesity: analysis of the National Diet and Nutrition Survey. Faculty of Medicine Research Conference, University of Southampton, Southampton, UK, June 2018

Glyn-Owen K, Parkes J, Harris S, Aspinall R, Roderick P. Redefining risk of liver disease in the general population: Analysis of the Health Survey for England 2016. European Association for the Study of the Liver (EASL), Vienna, Austria, April 2019. *Journal of Hepatology.* 2019 Apr 1;70(1):e35.

Glyn-Owen K, Parkes J, Harris S, Aspinall R, Roderick P. Redefining risk of liver disease in the general population: Analysis of the Health Survey for England 2016. Faculty of Medicine Research Conference, University of Southampton, Southampton, UK, June 2019.

Conference poster presentations

Glyn-Owen K, Böhning D, Parkes J, Roderick P, Buchanan R. The combined effect of alcohol and obesity on risk of liver disease: a systematic review and meta-analysis. Annual meeting, British Association for the Study of the Liver (BASL), Glasgow, UK, September 2019.
Chosen as one of top posters, selected for 'Best of BASL'.

Glyn-Owen K, Böhning D, Parkes J, Roderick P, Buchanan R. The combined effect of alcohol and obesity on risk of liver disease: a systematic review and meta-analysis. The Liver Meeting, American Association for the Study of Liver Diseases (AASLD), Boston, USA, November 2019. HEPATOLOGY 2019 Oct 1 (Vol. 70, Issue S1, pp. 753A-753A).

Signed: .....

Date: 9th April 2020 .....

Acknowledgements

I am very grateful for the wisdom, patience, support and encouragement that I have received every step of the way from my supervisors Julie Parkes, Paul Roderick and Richard Aspinall. They have not faltered on this long journey and without their support, I might have done so. Thank you.

I would like to thank the many occupants, past and present, of room AC22. The stimulating discussions, advice, support and good humour that they have provided during the last four years have been one of the highlights of my time as a postgraduate student. I hope that the many friendships forged will endure and that we will continue to encourage each other to pursue excellence in research and to put patients first.

I have been very fortunate to engage in several rewarding collaborations during my time working on this thesis. Thank you to all my co-authors on the presentations and publications listed here. They have been a pleasure to work with and I have learned a great deal from all of them. In particular Dankmar Böhning and Scott Harris, both brilliant statisticians and teachers who have been very generous with their time and knowledge. I hope that we may collaborate again in future.

I would like to thank all the authors who responded positively to my request for extra data, from published studies which met the criteria for the meta-analysis in Chapter two. For a junior researcher, evidence of this willingness to collaborate in the interests of good research and for no personal gain, was both reassuring and uplifting. Thank you to Fredrik Åberg, Sarah Floud, Carol Hermon, Bette Liu, Katherine McGlynn, Jackie Porcel, Andreas Schult, Veronica Wendy Setiawan and Jake Thistle.

Thank you to Matt Johnson, David Culliford and everyone in the Wessex CLAHRC team, for their help and cooperation in enabling this work. Also to the NIHR CLAHRC Wessex for giving me the opportunity. I would like to thank the participants of the Health Survey for England, the National Diet and Nutrition Survey, and all the cohort studies included in chapter 2, without whom this work would not have been possible.

Lastly but most importantly, I would like to thank all my family for their constant support. They inspire me every day and remind me how very much I have to be thankful for.

This thesis is dedicated to John Emmerson and Sophie Chapman.

Abbreviations

ARLD	Alcohol Related Liver Disease
ALT	Alanine aminotransferase
APRI	Aspartate aminotransferase to platelet ratio index
AST	Aspartate aminotransferase
AST:ALT	AST to ALT ratio
BARD	BARD score
BAFLD	Both Alcohol and Fatty Liver Disease
BMI	Body Mass Index
BSG	British Society of Gastroenterology
CI	Confidence Interval
CLD	Chronic Liver Disease
DALYs	Disability Adjusted Life Years
ELF®	Enhanced Liver Fibrosis test
FIB-4	Fibrosis 4 score
Fibroscan®	Transient elastography, proprietary
HCC	Hepatocellular Carcinoma
HSE	Health Survey for England
NAFLD	Non-alcoholic fatty liver disease
NASH	Non-alcoholic steatohepatitis
NDNS	National Diet and Nutrition Survey
NPV	Negative Predictive Value
NHS	National Health Service

TE	Transient elastography
UK	United Kingdom
USA	United States of America
WHO	World Health Organisation

Chapter 1: Background and aims

1.1 Overview

Liver disease is the third most common cause of premature death in the United Kingdom (UK), and across Europe mortality occurs mainly in people under 65 years.[1 2] Mortality from liver disease in the UK has increased 400% over the last 40 years, a dramatic increase during a time over which mortality from most other chronic diseases has decreased (Figure 1).

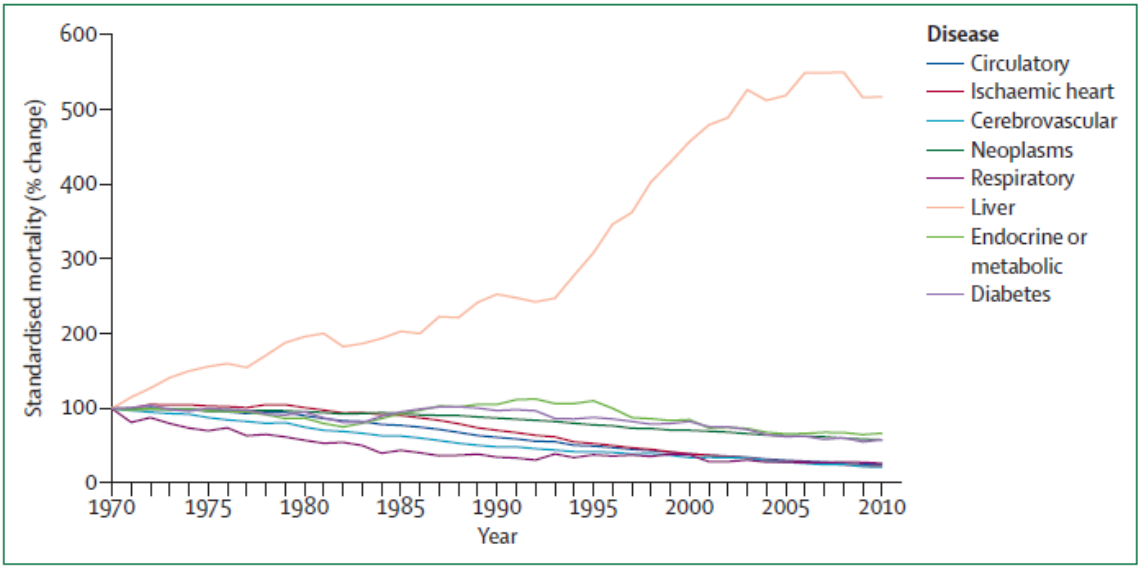


Figure 1: Standardised UK mortality rate data. Data were normalised to 100% in 1970 and subsequent trends plotted. Data were taken from the WHO-HFA database in 2014. Figure taken from The Lancet Commission[2]

The liver is an important abdominal organ, which carries out a large number of essential functions in the human body. The liver has a role in energy storage, fat digestion, blood clotting and removal of waste products such as alcohol, toxins or drugs.[3]

Liver disease has been described as the 'silent killer', as symptoms do not occur until disease is severe and irreversible. Patients present late to healthcare services, and 17% of patients with cirrhosis (end stage liver disease) die within one year of their first hospital admission.[4] More than 90% of deaths from liver disease are due to three potentially modifiable causes: Alcohol consumption, obesity and viral hepatitis.[1 2 5]

Chapter 1

This work focuses on chronic liver disease (CLD) due to alcohol consumption and obesity. The prevalence of obesity continues to rise, with associated Non-Alcoholic Fatty Liver Disease (NAFLD) affecting one in four people in Western countries.[6 7] Alcohol consumption per capita is highest in the World Health Organisation (WHO) European Region.[8] There are some encouraging trends, with the percentage of drinkers and per capita consumption both decreasing in the European region since 2010.[8] However, more than half of the European population still consume alcohol and harms from a given quantity of alcohol are known to be greater for the most deprived.[8] Alcohol related liver disease (ARLD) is estimated to cause 60% of all liver disease in the UK and 84% of liver deaths.[9]

The problems of alcohol consumption and obesity are not going away. However, liver disease caused by alcohol consumption and obesity is preventable and, if detected in its early stages, the liver may recover.[10 11] Understanding how BMI and alcohol affect risk, and identifying those at risk of liver disease is a fundamental step towards prevention.

1.2 Liver anatomy and function

The liver is a large organ in the right upper quadrant of the abdomen. It weighs approximately 1.5kg in an adult. The anatomy of the liver is described as two lobes, left and right, and eight segments. Within each segment are functional units called lobules. Within each lobule are many subunits called sinusoids. The key cellular elements within sinusoids are: Hepatocytes, Endothelial lining cells, Stellate cells and Kupffer cells.

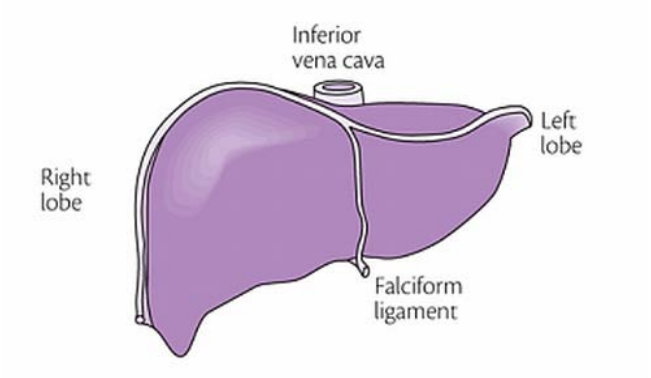


Figure 2: Left and right lobes of the liver[12]

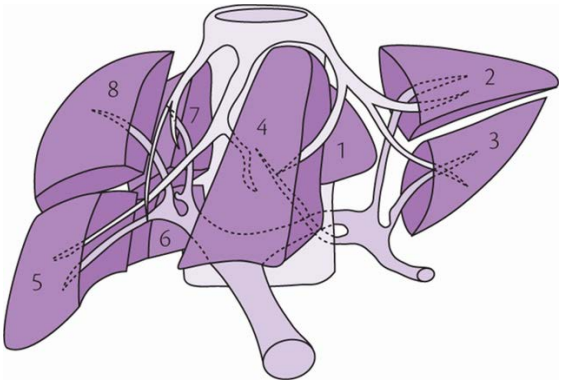


Figure 3: Functional anatomy of the liver showing segments[12]

The liver has a number of important functions: Bile, produced in hepatocytes, is involved in: maintaining gut pH; digesting fats; absorption of fat soluble vitamins; excretion of cholesterol and other toxins such as drugs, alcohol and heavy metals.[12] The liver also has a central role in: maintaining steady blood glucose levels through metabolism of carbohydrates; synthesising plasma proteins (including factors essential for blood clotting); controlling plasma concentrations of amino acids; clearing ammonia and bilirubin.[12]

1.3 Chronic Liver disease (CLD)

1.3.1 Classification of chronic liver disease

The most common causes of chronic liver disease are: alcohol misuse, non-alcoholic fatty liver, chronic hepatitis B infection (HBV), chronic hepatitis C infection (HCV), autoimmune hepatitis, metabolic/genetic liver disease.[13] Of these, alcohol misuse, non-alcoholic fatty liver and viral hepatitis infection account for more than 90% of chronic liver disease. This work focuses on liver disease caused by alcohol consumption and obesity, with a pragmatic approach that is not limited by formal classification of disease. The classification of liver disease with aetiologies relating to fat or alcohol are summarised in Table 1.

Table 1: ICD 10 codes for liver disease with aetiologies relating to fat or alcohol[14]

ICD 10 codes for liver disease	
K70	**Alcoholic liver disease**
K70.0	Alcoholic fatty liver
K70.1	Alcoholic hepatitis
K70.2	Alcoholic fibrosis and sclerosis of liver
K70.3	Alcoholic cirrhosis of liver - Alcoholic cirrhosis NOS
K70.4	Alcoholic hepatic failure Alcoholic hepatic failure: • NOS • acute • chronic • subacute • with or without hepatic coma
K70.9	Alcoholic liver disease, unspecified
K74	**Fibrosis and cirrhosis of liver**
K74.0	Hepatic fibrosis
K74.6	Other and unspecified cirrhosis of liver Cirrhosis (of liver): • NOS • cryptogenic • macronodular • micronodular • mixed type • portal • postnecrotic
K75	**Other inflammatory liver diseases**
K75.8	Other specified inflammatory liver diseases - Non-alcoholic steatohepatitis (NASH)
K76	**Other diseases of liver**
K76.0	Fatty (change of) liver, not elsewhere classified - Non-alcoholic fatty liver disease (NAFLD)
C22	**Malignant neoplasm of liver and intrahepatic bile ducts**
C22.0	Liver cell carcinoma - Hepatocellular carcinoma (HCC) - Hepatoma

The current categorisation of liver disease, as seen in Table 1, has evolved over time rather than being designed to fit with current knowledge. Alcoholic liver disease is well categorised, with sub categories relating to type and severity of disease - for example alcoholic fibrosis or alcoholic cirrhosis. Fatty liver disease is less well described, possibly as a result of the rapidity with which it has become prominent. The prevalence of disease defined as Non-alcoholic fatty liver disease (NAFLD) has increased dramatically over the last 50 years, alongside the increase in obesity. NAFLD now affects one in four people in western countries[6 7]. However, in the ICD classification it does not have its own category but comes under 'other diseases of liver'. NAFLD has only been included as a specific entity since the 2010 version of ICD-10. Non-alcoholic steatohepatitis (NASH), the more severe sequela of NAFLD, is under a separate category 'other inflammatory liver diseases'. Neither of these categories has sub categories to include fibrosis or cirrhosis as a result of fatty liver, which would therefore come under the generic K74 category. Whereas alcoholic fibrosis and cirrhosis have specific categories. This has implications for data on the epidemiology of disease.

Another limitation of the ICD disease classification, is that there is no category reflecting disease due to both alcohol consumption and NAFLD. The K70.0 'alcoholic fatty liver' category relates to fatty deposits in the liver as a result of alcohol abuse. This is not the same as alcohol consumption in someone who already has NAFLD as a result of being overweight or obese. Again this has implications for the epidemiological data, as the current classifications do not allow for the co-existence of alcohol related and non-alcoholic fatty liver disease. The 'non-alcoholic' in NAFLD describes the aetiology of disease, not the behaviour of the patient, but this is clearly confusing. This classification may also have contributed to clinical diagnoses and pathways remaining separate for alcohol related and 'non-alcoholic' liver disease. There is currently no formal or widely recognised terminology for people who have liver disease with both aetiologies.

Hepatocellular carcinoma (HCC) is the most common primary liver cancer. It is the third leading cause of cancer death worldwide. HCC is associated with the presence of chronic liver disease and sustained inflammatory liver damage.[15] It is a leading cause of death in patients with cirrhosis.[15]

1.3.2 Mechanism of liver damage

When liver damage occurs, all the vital functions of the liver are impaired. The first physical sign of liver disease may be jaundice, a yellow discolouration which is first seen in the sclera of the eyes and progresses to include the skin and soft palate. Jaundice is caused by excessive levels of bilirubin in the blood, which build up due to hepatic dysfunction.

The liver is a resilient organ and can repair itself extensively. Eventually, repeated insults, from any aetiology, result in the healing process becoming disturbed and chronic pathological fibrogenesis occurs.[13] Chronic liver disease progresses over time. Extracellular matrix is laid down, the liver becomes increasingly fibrotic and ultimately develops cirrhosis, or scarring. At this point the functions of the liver are significantly impaired and the damage is irreversible (Figure 4). Fibrosis stages F1 and F2 may be reversible, and research is ongoing to understand the degree of reversibility of liver fibrosis.[11 13]

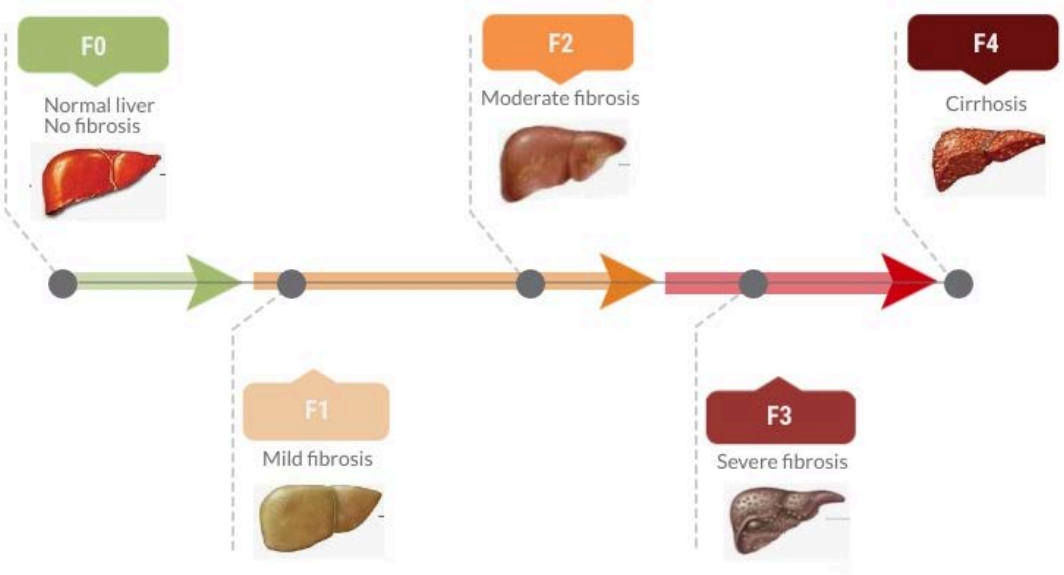


Figure 4: Progression of chronic liver disease (liver images credit[16])

The amount of time taken to progress from F1 to F4 is very variable, with some patients progressing rapidly and others so slowly that they never reach F4. Predicting which patients will progress rapidly is currently a key priority for clinical research.

There is no cure for chronic liver disease, excepting viral hepatitis where advances in viral eradication may lead to long-term cure. Liver transplantation is possible for end-stage disease, but donated organs are limited and patients at this stage are systemically extremely frail. After liver transplant in the UK, on average 94% of patients survive one year and 83% five years.[17] Ten year survival is around 64%.[18] The mainstay of efforts to reduce liver disease should focus on prevention, by behaviour change to reduce exposure to risk factors.

1.4 Measurement of liver function and damage

Physical signs and symptoms of liver disease do not appear until disease is advanced. They are a result of complications of cirrhosis. There are many different methods used to assess liver function and damage, but there is no perfect test. Some of the available methods, including those referred to during this thesis, are summarised, with their advantages and disadvantages, in Table 2.

Table 2: Selection of commonly used methods for assessing liver fibrosis, including all those referred to in this thesis[19 20]

	How does it work?	Advantages	Disadvantages	Use
Liver blood tests – most commonly used in the context of chronic liver disease				
ALT (Alanine aminotransferase)	Measure of hepatocyte damage	Standard laboratory test	- Not liver specific. May be raised due to medications e.g. Statins and in non-liver conditions. - Does not assess fibrosis	All aetiologies
AST (Aspartate aminotransferase)	Measure of hepatocyte damage	Standard laboratory test	- Non-specific. Present in cardiac muscle, skeletal muscle, kidneys, brain and red blood cells as well as the liver. - May be raised in non-liver related conditions. - Does not assess fibrosis	All aetiologies
Non-invasive markers (many more are available[21] – these are some of the most commonly used)				
DIRECT				
ELF test	Calculated using P3NP, hyaluronate, TIMP-1	- Non-invasive - Easily repeatable - No contraindications - Can be performed in any setting	- Proprietary test, with cost implications - Not available in all areas depending on commissioning arrangements	HCV, NAFLD
INDIRECT				
FIB-4 (Fibrosis 4 score)	Calculated as: (age in yrs x AST) / (platelet count x √ALT).[22]	- Non-invasive - Easily repeatable - No contraindications - Can be performed in any setting - Uses standard laboratory tests and basic patient information.	- Age sensitive. Different cut offs suggested for older people. - Not validated in ALD. - Does not distinguish between intermediate stages of fibrosis	HBV, HCV, NAFLD
APRI (Aspartate aminotransferase to Platelet Ratio Index)	Calculated as: (AST(IU/L)/AST upper limit of normal) / platelets(x10^9/L)] x 100[23]	- Non-invasive - Easily repeatable - Uses standard laboratory tests.	- Does not distinguish between intermediate stages of fibrosis	All aetiologies

	How does it work?	Advantages	Disadvantages	Use
AST:ALT ratio	Calculated as: AST(IU/L)/ALT(IU/L)	- Non-invasive - Easily repeatable - No contraindications - Can be performed in any setting - Uses standard laboratory tests.	- Does not distinguish between intermediate stages of fibrosis	HBV, HCV, NAFLD
Diagnostic imaging (more available[21] – these are some of the most commonly used)				
Ultrasound	Transducer sends ultra high frequency sound waves, and detects echoes that return. Generates 2D images.	- Non-invasive - Can assess steatosis, inflammation	- Operator must be highly trained - Cannot give indication of degree of fibrosis	Mostly used to assess fatty liver
Fibroscan® TE (Transient Elastography)	The transducer sends vibrations to the liver. The speed of the wave passing through the liver indicates tissue stiffness	- Non-invasive and not harmful - Immediate results - Reproducible and easily repeatable - Assesses physical properties of the liver - Outpatient setting - Minimal training - No contraindications - May have prognostic, as well as diagnostic, value	- False positives during acute hepatitis, extra-hepatic cholestasis, liver congestion, food intake, xs alcohol intake - Cannot distinguish between intermediate stages of fibrosis - Less accurate if patient BMI>30, ascites - Failure in around 5% cases - Operator experience dependent	All aetiologies
Magnetic Resonance Elastography (MRE)	Mechanical waves used to assess tissue stiffness	- High sensitivity and specificity	- Time consuming - Expensive	All aetiologies
Liver biopsy				
Liver biopsy	Percutaneous core biopsy taken from the liver and studied by a Histopathologist.	- Reference standard accuracy - Direct assessment of fibrosis - Well established staging system for reporting - Can also assess degree of inflammation, steatosis	- Invasive and sometimes painful - Potentially harmful. Mortality 0.01% - Variability in core samples & observer assessments - Cannot be regularly repeated - Requires hospital admission - Contraindicated in some patients	All aetiologies

The reference standard method for directly observing and assessing fibrosis is liver biopsy. However, biopsy is invasive, potentially harmful and must be performed in hospital. It is also not a perfect reference standard, as its performance is affected by sampling error, intra-observer variability, inter-observer variability, discordance within the biopsy sample and degree of experience of the pathologist.[19] When considering alternative methods, it is worth noting that these limitations in the reference standard affect the performance assessment of any other test which is compared to biopsy. For example, the area under the receiver operator characteristic curve (AUROC) is often used to assess the performance of non-invasive markers. A perfect AUROC score would be 1.0. Even if a marker were actually perfect, it may not achieve an AUROC score of more than 0.9 if liver biopsy was used as the reference standard.[19 20]

Diagnostic imaging works by assessing the degree of tissue stiffness, thus providing an estimate of fibrosis, or by observing the amount of fat deposited in the liver. Liver blood tests, such as liver enzymes ALT and AST, measure the quantity of these enzymes found in serum. Non-invasive markers can be direct or indirect. Direct markers measure substances in the serum which are directly related to the process of fibrosis, for example hyaluronic acid which is produced in the deposition of extracellular matrix leading to fibrosis, whereas indirect markers are changed secondary to fibrotic processes. Indirect markers may be combined with other markers or with patient information, in a 'panel' to produce an overall 'fibrosis score'. For example the Fibrosis-4 (FIB-4) score, which is calculated as (age in yrs x AST) / (platelet count x √ALT).[22]

Non-invasive markers, such as liver blood tests and fibrosis scores, are the most commonly used method to try and detect early liver disease, before symptoms develop. Some are available in primary care and easy to calculate where necessary. They are easily repeatable, reproducible, pose no risk to the patient and do not rely on operator factors. Blood tests ALT and AST have a reference range, which is defined by the processing laboratory, and any result above the upper level is considered abnormal. The reference range varies between laboratories and is often different for males and females. Fibrosis scores such as FIB-4 and ELF®, have had thresholds set for 'ruling-in' or 'ruling-out' fibrosis, based on their sensitivity and specificity. The sensitivity of a test is a measure of the test's ability to correctly identify as having disease, all those people who do have the disease (these people are called true positives). The specificity of a test is a measure of the test's ability to correctly identify as not having disease, all those people who do not have disease (these people are called true negatives). Finding the optimum threshold to balance sensitivity and specificity is challenging. For example, in one cohort if the threshold for the AST:ALT ratio was set at 0.8, sensitivity for the test detecting advanced fibrosis was 74%, and specificity 78%. If the threshold was set at 1.0, sensitivity for the test detecting advanced fibrosis

was 52% and specificity 90%.[24] Despite their many advantages, these tests are limited in their ability to detect fibrosis and to differentiate between intermediate levels of fibrosis. For many, their strongest feature is their negative predictive value - their ability to rule out fibrosis.

The performance of some of the most commonly used non-invasive tests are shown in Table 3. The ideal test would have 100% sensitivity (no cases missed) and 100% specificity (no cases wrongly identified). As can be seen from Table 3, the performance of tests varies depending on the underlying aetiology of liver disease, the stage of fibrosis being detected and the thresholds used. As discussed earlier, the performance of these tests is limited by the imperfection of liver biopsy as the reference standard.

Another important limitation to consider, is that these tests have been designed and validated in populations with known liver disease. These patient populations are highly selected. They differ from each other, as well as from the general population. For example, the sensitivity and specificity of a fibrosis test in a population of patients with Hepatitis C, may differ considerably from the test's performance in a population of patients with NAFLD. This is called Spectrum Bias.

The sensitivity and specificity of a test depends on the spectrum of patients among whom the test assessments are conducted.[25] Tests need to be validated amongst the broadest possible spectrum of patients in which they will be used. A test which is going to be used amongst the general population therefore, must have its sensitivity and specificity tested amongst the general population. There are three main categories across which features must be adequately broad: pathology, clinical features and co-morbidity. Failure to validate a test in an adequately broad range of patients leads to errors in assessing the value of the test, due to spectrum bias. A test may be positive amongst those with severe disease, but negative amongst those with mild disease, or in those with certain co-morbidities.[25] In the context of liver disease, if the population in which a test is assessed is skewed to the extreme ends of the spectrum of fibrosis (F0 and F4), then the test will appear to have a higher sensitivity and specificity than if the disease in the population was predominantly of middle severity (F1 and F2).[20] None of the non-invasive tests in Table 3 have been designed or validated in general population settings. Their performance in a general population setting therefore remains unclear.

In summary, there is no currently no perfect test or marker to diagnose chronic liver disease. It is necessary to work within the scope of these imperfections, in order to try and achieve the best outcomes for patients.

Table 3: Diagnostic accuracy of selected non-invasive tests for detection of fibrosis in patients with NAFLD/NASH, ALD and cirrhosis of any cause[26]

Test	Number of studies	Cut-off	Summary Sensitivity (95% CI)	Summary Specificity (95% CI)
NAFLD/ NASH – detection of fibrosis ≥ F3				
APRI	4	0.5-1.0	0.40 (0.07 to 0.86)	0.82 (0.78 to 0.6)
AST:ALT ratio	4	0.8	0.79 (0.51 to 0.91)	0.70 (0.55 to 0.82)
AST:ALT ratio	3	1.0	0.46 (0.29 to 0.65)	0.91 (0.85 to 0.95)
BARD score	7	2	0.84 (0.69 to 0.93)	0.61 (0.47 to 0.73)
NAFLD fibrosis score (low cut-off)	10	-1.455	0.80 (0.67 to 0.89)	0.66 (0.57 to 0.74)
NAFLD fibrosis score (high cut-off)	9	0.676	0.40 (0.20 to 0.64)	0.97 (0.94 to 0.98)
FIB-4	4	1.3–1.92	0.84 (0.75 to 0.90)	0.74 (0.64 to 0.83)
FIB-4	2	3.25	0.38 (0.22 to 0.57)	0.97 (0.92 to 0.99)
ELF®	1	10.35	0.80 (0.65 to 0.89)	0.90 (0.84 to 0.94)
Hyaluronic acid	4	46-50	0.88 (0.58 to 0.97)	0.82 (0.75 to 0.87)
Fibroscan®	8	7.5-10.4	0.82 (0.74 to 0.88)	0.84 (0.78 to 0.89)
NAFLD fibrosis score and ELF combined (low cut-off)	1		0.91 (0.79 to 0.96)	0.96 (0.91 to 0.98)
NAFLD fibrosis score and ELF combined (high cut-off)	1		0.86 (0.73 to 0.94)	0.99 (0.96 to 1.00)
ALD – detection of fibrosis ≥ F2				
APRI	2	1.5	0.54 (0.42 to 0.66)	0.78 (0.64 to 0.88)
APRI	2	0.5	0.72 (0.6 to 0.82)	0.46 (0.33 to 0.6)
Fibroscan®	1	7.8	0.81 (0.7 to 0.88)	0.92 (0.76 to 0.98)
ALD – detection of fibrosis ≥ F3				
APRI	1	2.0	0.40 (0.22 to 0.61)	0.62 (0.41 to 0.79)
Fibroscan®	4	11.0-12.5	0.87 (0.64 to 0.96)	0.82 (0.67 to 0.91)
Cirrhosis any cause				
APRI	27	0.75-1	0.75 (0.71 to 0.8)	0.78 (0.75 to 0.81)
APRI	23	2	0.45 (0.37 to 0.52)	0.93 (0.9 to 0.95)
AST:ALT ratio	13	1	0.49 (0.39 to 0.59)	0.87 (0.75 to 0.94)
FIB-4	5	1.45-1.92	0.84 (0.76 to 0.89)	0.71 (0.62 to 0.79)
FIB-4	4	3.25-4.44	0.42 (0.2 to 0.69)	0.92 (0.58 to 0.99)
ELF®	1	9.4	0.93 (0.69 to 0.99)	0.79 (0.67 to 0.88)
Hyaluronic acid	8	78-237	0.81 (0.65 to 0.9)	0.88 (0.8 to 0.94)
Fibroscan®	65	9.2-26.5	0.89 (0.86 to 0.91)	0.89 (0.87 to 0.91)

NAFLD – Non-alcoholic fatty liver disease
NASH – Non-alcoholic steatohepatitis
HCC – Hepatocellular Carcinoma
ARLD – Alcohol Related Liver Disease
APRI – AST to Platelet Ratio Index
ELF – Enhanced Liver Fibrosis score
FIB-4 – Fibrosis 4 score

1.5 Chronic liver disease epidemiology

This thesis focuses on the public health problem of chronic liver disease due to alcohol consumption and obesity – both modifiable, and therefore potentially preventable, risk factors. This type of liver disease has historically been categorised as two distinct diagnoses: 'Alcohol Related Liver Disease' (ARLD) and 'Non-Alcoholic Fatty Liver Disease' (NAFLD). In reality, the underlying disease mechanism is very similar and often both risk factors are present in the same patient. Both alcohol consumption and obesity risk factors may also occur in the presence of viral hepatitis.

1.5.1 Global

Chronic liver disease, measured as cirrhosis, was responsible for 41 million Disability Adjusted Life Years (DALYS) globally in 2017. This represents an age-standardised rate of 1071 DALYS per 100,000 people.[27] The global mortality rate due to cirrhosis in 2010 was 16 deaths per 100,000 population, with a similar proportion of liver disease attributable to Hepatitis B infection, Hepatitis C infection and alcohol misuse[28]. Cirrhosis due to underlying fatty liver disease was not separately categorised in the Global Burden of Disease Study before 2017. In 2017, the proportion of cirrhosis/CLD due to underlying aetiologies was 29% hepatitis B, 25% hepatitis C, 25% alcohol misuse, 8% Non-alcoholic Steatohepatitis (fatty liver disease) and 12.5% other causes.[27]

Cirrhosis was in the top ten causes of DALYS for Central Europe region and Central Asia region in 2010 and it was ranked as the 23rd leading cause of DALYS worldwide.[29] It was the 12th leading cause of death worldwide in 2010, and was in the top ten causes of Years of Life Lost (YLL) for High-Income Asia Pacific, Western Europe, Eastern Europe, Central Europe, High-Income North America, Southern Latin America, Tropical Latin America, Central Latin America, Central Asia, North Africa and the Middle East.[28] There was a 27% increase in Global YLLs due to cirrhosis, between 1990 and 2010.[28]

Males are more likely to suffer from cirrhosis than females. For females worldwide, cirrhosis was the 28th leading cause of DALYs in 1990, the 30th leading cause in 2007 and the 26th leading cause in 2017. For males worldwide, cirrhosis was the 15th leading cause of DALYs in 1990, the 13th leading cause in 2007 and the 11th leading cause in 2017.[27] In 2010, cirrhosis was responsible for one million deaths worldwide and for 3.6% of all deaths in 15-49 year old males.[28]

Global deaths due to cirrhosis have decreased over the last 30 years, from 20 per 100,000 to 16 per 100,000 but trends vary between regions. Increased vaccination and treatment of viral

hepatitis have led to reductions in mortality rates in some areas, but ARLD deaths have increased in others. Non-alcoholic fatty liver disease (NAFLD) and its sequela, non-alcoholic steatohepatitis (NASH) are increasingly contributing to the burden of cirrhosis, with global prevalence of NAFLD estimated at 25%.[30] NAFLD is associated with overweight/obesity, rates of which have tripled since 1975, with current estimates suggesting that 39% of the population globally are overweight and 13% are obese.[30] It is also associated with type 2 diabetes, with more than 60% of type 2 diabetes patients also having NAFLD.[30] Type 2 diabetes is also increasing globally, with predictions that the current prevalences of 8.4% (women) and 8.9% (men) will both reach 9.9% by 2045.[31]

1.5.2 Europe

As a region, Europe has a higher prevalence of liver disease than any other. However, there is considerable variation between countries with age-adjusted prevalence ranging from 447 to 1,100 cases per 100,000 in 2016.[5] In Central Europe cirrhosis is in the top ten leading causes of DALYS, in Western Europe it is ranked 19th and in Eastern Europe at number 11.[29] In Western countries the predominant aetiology was Alcohol Related Liver Disease; in central Europe alcohol and viral hepatitis were both dominant; in Eastern Europe viral hepatitis was the most common underlying cause but these data did not include fatty liver disease as a separate category.[5] The prevalence of NAFLD in Europe is estimated at 24%, with higher prevalence in Southern Europe compared to the North.[30]

Mortality from liver disease also varies widely between European countries, but deaths occur predominantly in younger people – two thirds of liver deaths are in people under 65 years old.[5 28] From 1970 to 2015, mortality rates from liver disease have decreased in Austria, Croatia, France, Germany, Greece, Italy, Luxembourg, Portugal, Slovenia, Spain and Switzerland. Rates have increased in Bulgaria, Estonia, Finland, Hungary, Kazakhstan, Latvia, Lithuania, Romania and the UK. Mortality rates in Slovakia and Uzbekistan are high but unchanging, whereas rates are low and unchanging in Belgium, Cyprus, Czech Republic, Denmark, Iceland, Ireland, Malta, Netherlands, Norway, Poland, Serbia and Sweden.[5]

1.5.3 United Kingdom

The mortality rate from liver disease in the UK has dramatically increased over the last 30 years, in contrast to reductions seen in most other chronic diseases (Figure 1)[2]. Mortality from liver disease

increased from 13.9 to 16.6 per 100,000 population between 2001 and 2010.[32] Deaths from cirrhosis caused by alcohol misuse are higher in the UK than globally (Figure 5). Patterns vary across the UK, with Scotland being an area of high mortality (Figure 6). Alcohol was estimated to account for 70% of liver cirrhosis DALYS in England in 2013, although this figure is likely to vary between regions.[33] Alcohol related liver disease is estimated to cause 60% of all liver disease in the UK and 84% of liver deaths.[9]

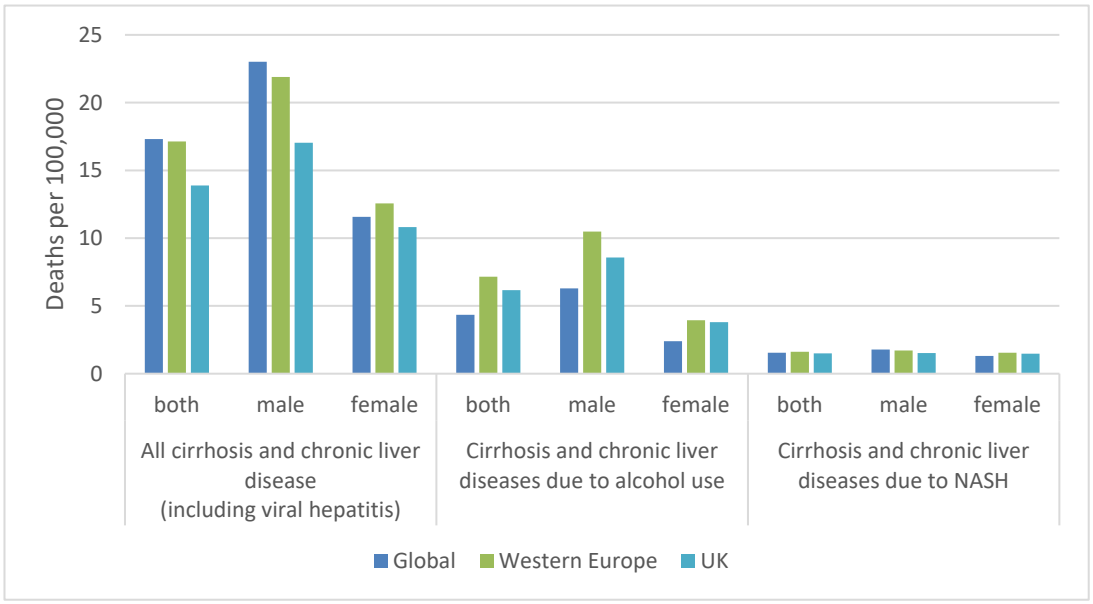


Figure 5: Deaths from cirrhosis in 2017, per 100,000 population, grouped by region, sex and underlying aetiology of liver disease. Data source: GBD compare[34]

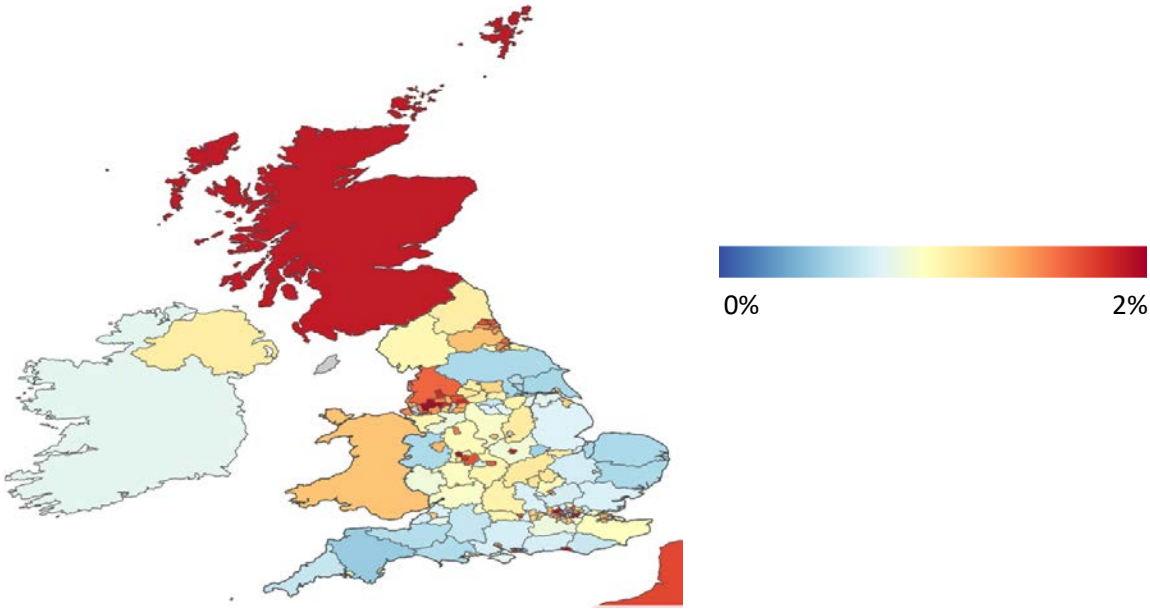


Figure 6: Percentage of total deaths due to cirrhosis and other chronic liver diseases in 2017. Visualisation and data source: GBD compare[34]

Liver disease now impacts most, on the most deprived in the UK and inequalities are widening.[2 9 35] Increases in death rates from cirrhosis between 1990 and 2013 were found to be largest in the most deprived areas,[33] with mortality from cirrhosis four times higher in the most deprived areas.[32] Figure 8 shows the increase in deaths from liver disease, and from all alcohol-related mortality, with increasing deprivation in the UK. This has not always been the case. There has been a significant change in the distribution of cirrhosis by indicators of deprivation over the last century. In 1921, rates were substantially higher in social class I and II. By 1991, this pattern had reversed with rates in social classes IV and V more than double those in social classes I and II.[36] People living in the most deprived areas are now almost twice as likely to have an alcohol related death, compared to those living in the least deprived areas.[37] This change was partly attributed to the affordability of alcohol, which used to be an 'expensive luxury' but which has in the second half of the century become dramatically cheaper and more readily available.[36] Alcohol was 60% more affordable in 2017, than it was in 1981.[9] However, this does not truly explain the association with deprivation, as alcohol consumption is now reported to be lower with increasing deprivation.[37 38] Figure 8 shows the increase in liver deaths with increasing deprivation, despite the proportion of increasing and higher risk alcohol consumers decreasing. Alcohol use is the fourth highest risk factor for DALYS in six out of the nine most deprived regions of England.[33] The association between deprivation and alcohol related mortality is statistically significant for both men and women, although stronger in men (Figure 7)[2]. There is an alcohol harm paradox,

whereby the most deprived in the UK suffer disproportionate harm from alcohol consumption, and liver disease forms a substantial part of that harm.[37 38]

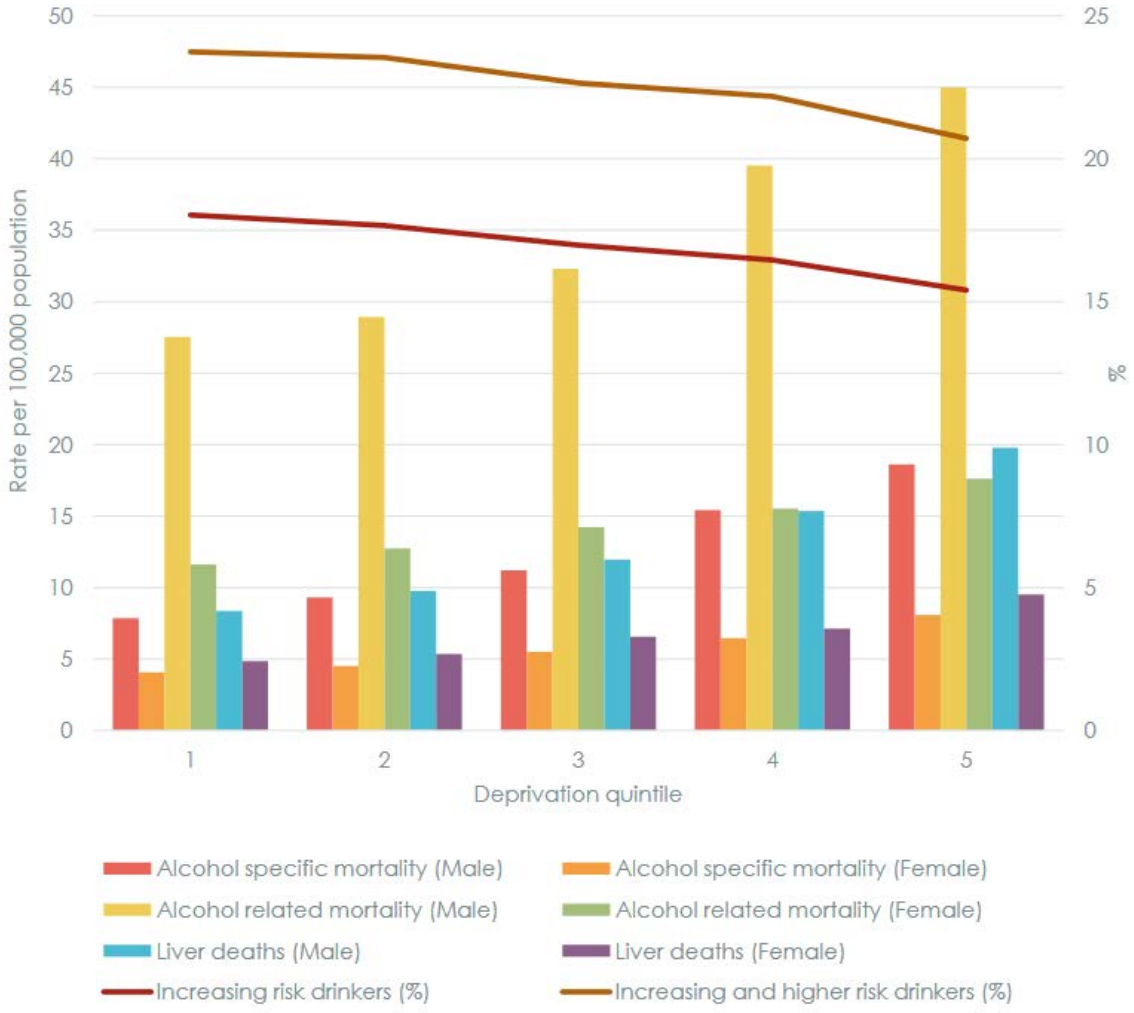


Figure 7: Variations in alcohol-related mortality and drinking patterns, by deprivation (Local Alcohol Profiles for England, Centre for Public Health, 2012)[37]. Quintile 1 = least deprived, quintile 5 = most deprived.

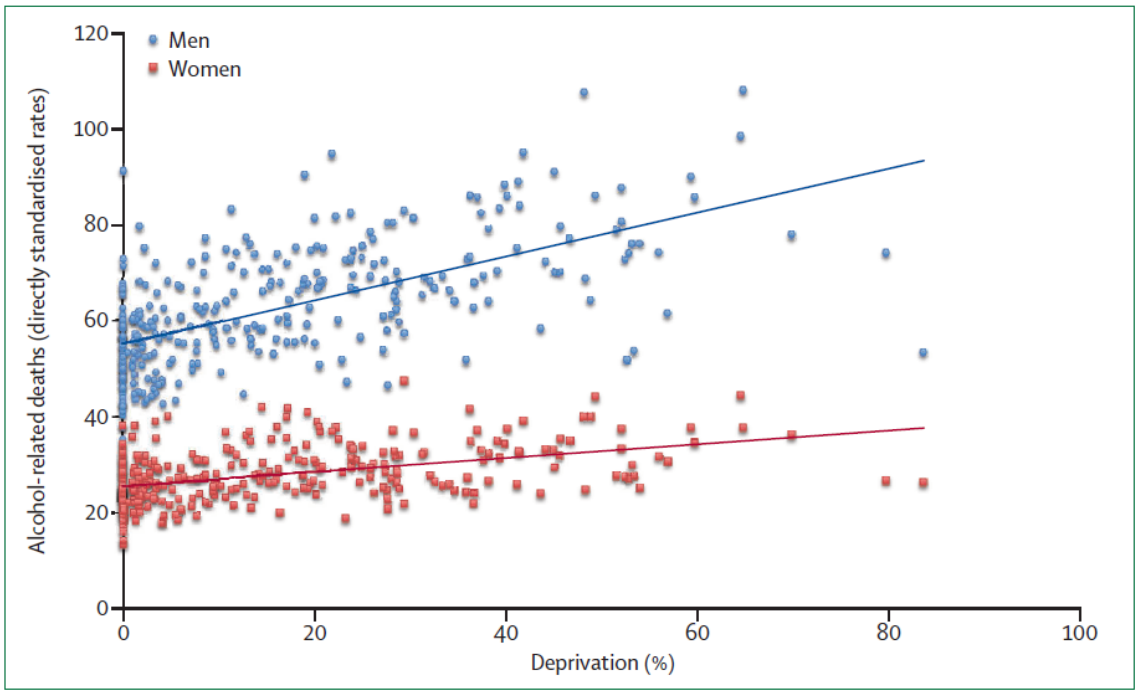


Figure 8: Alcohol-related deaths, directly standardised rates, for England in 2012 at local authority level. Data taken from Local Alcohol Profiles for England. Men $R^2 = 0.386$, $p<0.001$. Women $R^2 = 0.188$, $p<0.001$. Graph credit: Lancet Commission for Liver Disease[2]

Overweight and obesity are a continuing problem in the UK, with 64% of the population having a BMI ≥ 25.[39] This is one of the highest prevalences in Western Europe.[39] NAFLD is increasing in prevalence alongside the obesity epidemic, with models estimating 14.5 million cases prevalent annually in the UK.[40] Childhood obesity has increased every year, for the last half century, with a recent study finding steatosis (fatty liver) in 20% of unselected young people aged 22-26 years.[41] Obesity is also strongly linked to deprivation, with children from the most deprived areas in England much more likely to be overweight or obese than those from the least deprived areas.[9] This gap has widened consistently over the last thirty years.[9]

1.5.4 Gender

Males are more likely to have, and to die from cirrhosis than females, across all regions. Figure 5 shows deaths from cirrhosis, by sex, across regions and by underlying aetiology of cirrhosis. Cirrhosis due to alcohol use is more common in Western Europe and the UK than it is globally, for both males and females. Cirrhosis due to NASH is more common for females in Western Europe and the UK, than it is globally.

For females worldwide, cirrhosis was the 28th leading cause of DALYs in 1990, the 30th leading cause in 2007 and the 26th leading cause in 2017. For males worldwide, cirrhosis was the 15th leading cause of DALYs in 1990, the 13th leading cause in 2007 and the 11th leading cause in 2017.[27] In 2017, the rate of DALYs due to cirrhosis in males worldwide was 719 per 100,000 population. For females, the same rate was less than half at 308 per 100,000.[27] In 2010, cirrhosis was responsible for one million deaths worldwide and for 3.6% of all deaths in 15-49 year old males.[28]

1.5.5 Age

Liver disease deaths occur predominantly in working age people.[5 28] Estimates suggest more than 60% of liver deaths are in people under 70 years of age,[9] and it may be as high as two thirds of deaths in people under 65 years.[28] As a proportion of all deaths, there is a peak in deaths from cirrhosis from 30-69 years, across all regions and aetiologies (Figure 8). However, prevalence of chronic liver disease is higher in older people, probably due to its progressive nature. Both a higher prevalence of NAFLD and more severe fibrosis were found in people older than 60 years.[30]

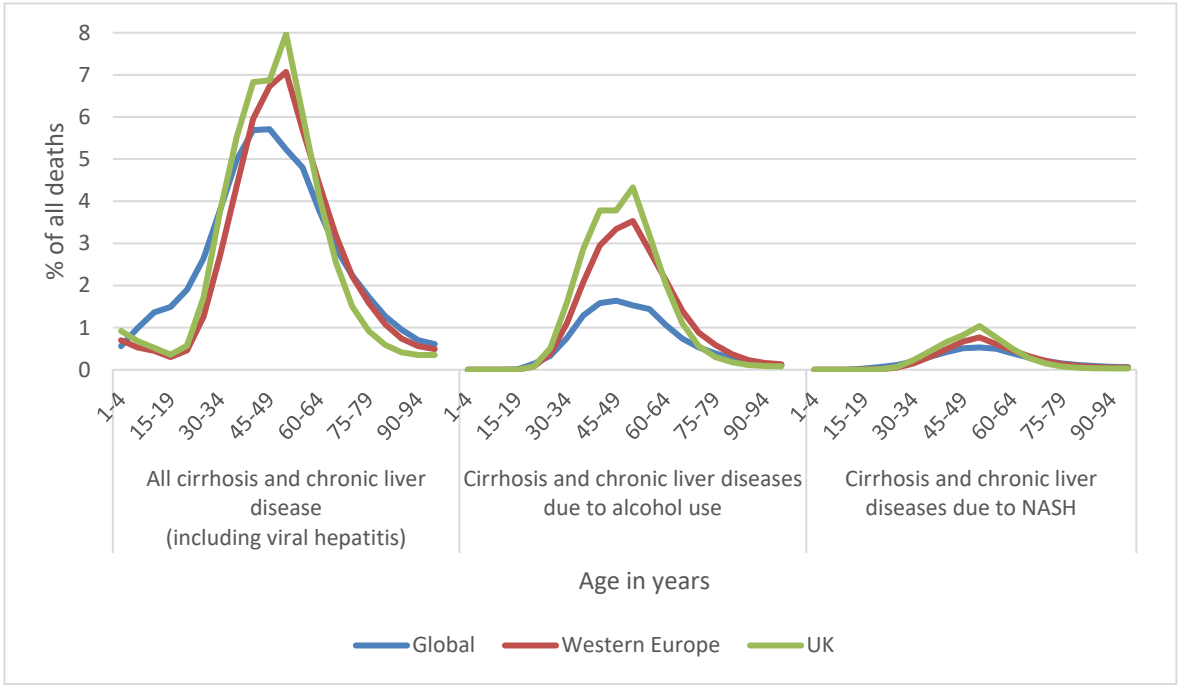


Figure 9: Percentage of all deaths which were due to cirrhosis in 2017, grouped by age, region and underlying aetiology of liver disease. Data source: GBD compare[34]

1.6 Financial costs of liver disease in the UK

The financial costs of liver disease are hard to quantify, as they cover many domains. As already discussed, liver disease deaths occur in younger people. An estimated 62,000 years of working life are lost to liver disease every year in the UK, so loss of productivity is a significant cost to the economy. There are also direct costs to the NHS for healthcare, as well as the opportunity cost that arises from money spent during the advanced stages of liver disease, which could have been prevented by early intervention to modify risk factors.

Two of the main causes of liver disease, alcohol and obesity, are also contributing factors to a large number of other chronic diseases including cancers, heart disease and dementia. Alcohol and obesity also have significant wider costs to society. By addressing these risk factors there are substantial financial savings to be made as well as huge prevention of harm. Estimates of the total annual cost of alcohol to UK society range from £20 billion to £55 billion.[2 9] For obesity, the estimates range from £27 billion to £46 billion per year.[9 42] These costs are increasing, with increasing prevalence of obesity. By 2035, projections indicate that 48% of men and 43% of women in the UK will be obese, and that the cost of loss of productivity alone will be £14 billion per year.[9]

1.7 Public Health and liver disease

The health, financial and societal arguments for action to prevent liver disease are clear. Prevention strategies are usually classified as:[43]

Primary prevention – preventing or delaying onset of disease in people at risk. For example vaccinations, changing risk behaviours in those without known disease.

Secondary prevention – identifying early disease in the population and acting to prevent or delay further progression. For example exercise programmes after myocardial infarction, low dose aspirin in those with cardiovascular disease.

Tertiary prevention – reducing long-term morbidity and mortality due to the disease. For example reducing allergen exposure in a person with asthma.

Public health action to prevent liver disease could take place at both the primary and secondary prevention levels. Prevention actions may be targeted towards the whole population 'population strategy', or towards groups at greatest risk of disease 'high risk strategy'. Geoffrey Rose suggested that because there are many more people in the population at low risk of a disease, they may in fact contribute more cases of the disease than those at high risk.[44] The implication of this is that if the whole population reduces their risk a little, the overall effect on reducing disease may be much greater, than if risk is reduced only in those few at greatest risk. This principle applies where a risk factor is very common through the population, so would apply to both overweight/obesity and alcohol consumption. Reducing these risk factors in the whole population may prevent more liver disease than focusing only on those at greatest risk.

The 'high risk' strategy targets prevention actions towards those at greatest risk of disease. This may be very effective – resources can be prioritised to those most at risk and health promotion messages can be tailored, so that they resonate with these risk groups. High risk strategies usually involve identification of individuals, with associated interventions at an individual level. However whole population interventions can differentially affect those at highest risk – for example Minimum Unit Pricing (MUP) of alcohol, which brings greatest benefit to those at highest risk of alcohol related harm.[45]

There are some significant potential pitfalls with a high risk approach. Defining the highest risk group is not always straightforward. In the context of liver disease, would this group be the highest risk alcohol consumers, the morbidly obese, or people with combined risk? There is also a real risk of stigmatising certain groups who are labelled as high risk; groups are not homogenous and people can rarely be categorised in terms of behaviours, or motivation for certain behaviours;

other health issues may be overlooked in groups deemed at high risk of a certain condition; and many people at risk will be missed by a targeted prevention strategy.[43] For example those who have a combination of alcohol and obesity risk factors might be missed, despite their increased risk of liver disease, if neither risk factor alone is high enough to trigger concern. In practise, strategies targeting the whole population and strategies targeting high risk groups can and do operate at the same time. For liver disease, this combination of approaches is probably necessary.

A key element of primary prevention strategies is health education and changing risk behaviours. Awareness of the risk factors for liver disease amongst the general population is known to be low.[46] A recent survey established that only 11% of a representative sample of British adults could identify the three main causes of liver disease.[47] Nearly half of participants either did not know, or over-estimated the UK Chief Medical Officer's recommended low-risk drinking level.[47] Effectiveness of education measures may be higher in those at high risk, than at the whole population level.

Secondary prevention involves detecting liver disease early, and acting to prevent or delay disease progression. This could be detecting liver disease early, before signs and symptoms appear and whilst disease is still reversible, and intervening to change risk behaviours and halt/reverse disease progression. As discussed earlier in this chapter, there are a wide range of tests available which try to detect early disease. These are imperfect and have not been designed or validated in general populations, which is where secondary prevention would primarily take place.

Government policy and legislation can help with both primary and secondary prevention measures, and in both 'population strategy' and 'high risk strategy' approaches. The Chief Medical Officer's guidance on safe levels of alcohol consumption are widely publicised and are printed on most alcoholic beverage labels. Changes in these guidelines could have wide reaching impact for the whole population. Legislation such as minimum unit pricing (MUP) for alcohol, would apply to the whole population but would be targeted particularly at those most at risk. Evidence shows that the greatest reduction in alcohol consumption due to MUP would be in harmful drinkers, and that the greatest health benefits as a result of MUP would be seen in the most deprived.[45] The UK government's 'sugar tax' on soft drinks, which came in to effect in 2018 and charges manufacturers a levy if the sugar content of their products is above certain thresholds, was a key action in their primary prevention measures to tackle obesity.

A summary of possible primary and secondary prevention measures for liver disease, at different levels of intervention, are shown in Figure 9.

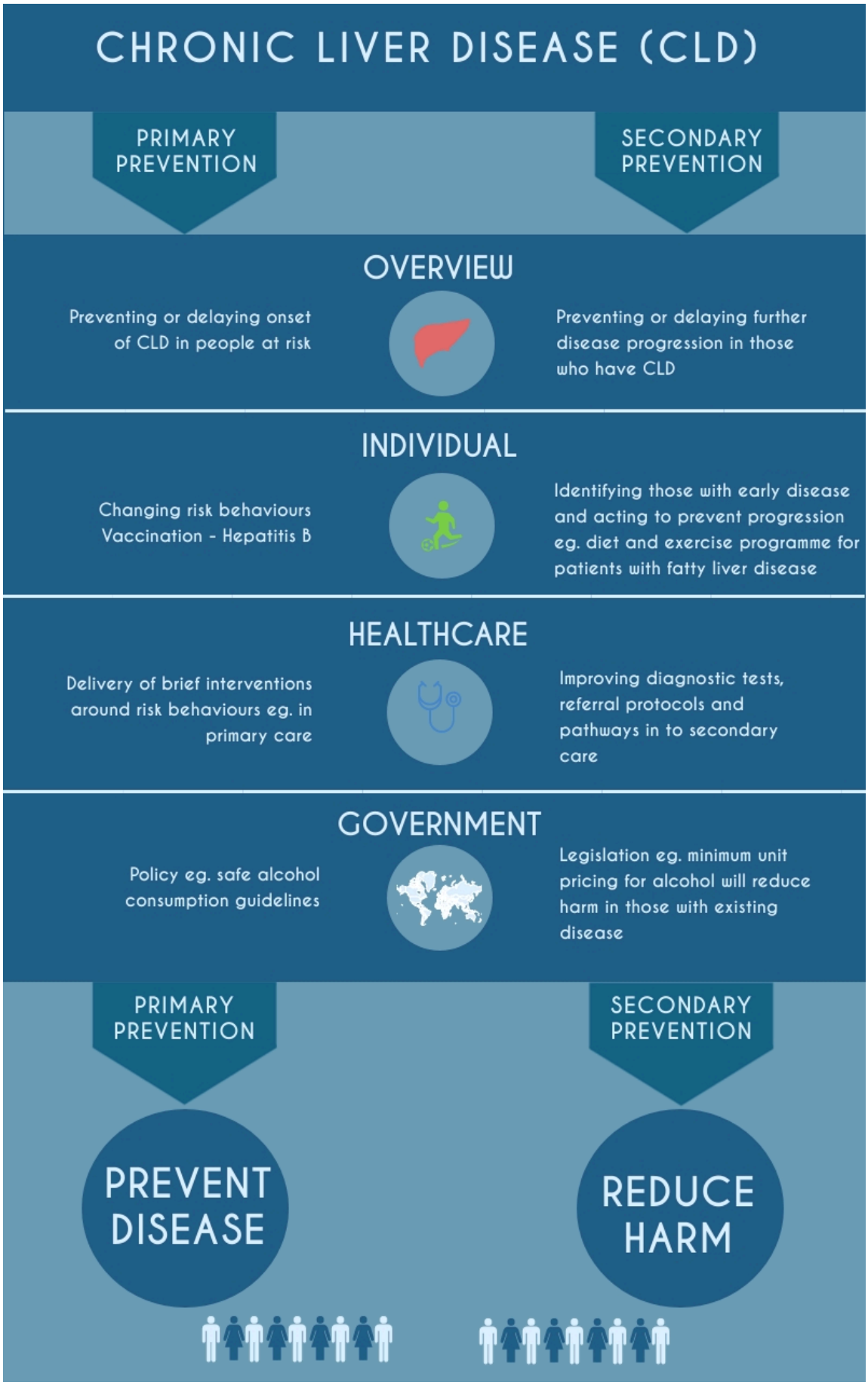


Figure 10: Examples of prevention strategies for chronic liver disease, by primary and secondary prevention and at different levels of intervention

Unhealthy lifestyle behaviours co-cluster in the population.[48] Mortality risk increases as the number of lifestyle risk factors increases. The majority of the UK population (nearly 70%) engage in two or more lifestyle risk factors.[48] Multiple lifestyle risk factors are more common in people who are male, younger, left education earlier and have lower socioeconomic position and these health inequalities are increasing over time.[48] Obesity and alcohol, two of the three main risk factors for liver disease, are both strongly linked to deprivation. Prevention approaches must be carefully designed, so that they do not widen health inequalities. The most deprived may be the least able to respond to suggested risk behaviour changes, such as a more healthy diet. Strategies to tackle obesity and alcohol consumption may be effective at the whole population level, but will also need targeting of interventions in more deprived areas. For example improving access to physical activity and outdoor spaces.

Obesity and alcohol are also risk factors for a number of other chronic diseases, including heart disease, some cancers and dementia. In developed countries such as the UK, 31% of DALYs and 44% of deaths are attributable to alcohol consumption, overweight, cholesterol, poor diet and physical inactivity.[49] The health of many patients is adversely affected by the dual risks of alcohol and obesity. At the population level, there are huge health gains to be made from even small overall reductions in BMI and alcohol consumption.

1.8 Screening for liver disease

Due to the high rates of premature mortality, the effectiveness of intervening early, and the lack of obvious signs or symptoms of disease, screening for liver disease in the general population has been suggested.[2 50] The purpose of screening is to reduce overall harm caused by a disease, by identifying those individuals in a population who are 'more likely to be helped than harmed by further tests'. The screening itself does not diagnose disease. In the case of liver disease, a screening test might be a non-invasive test such as those described in section 1.4, whereas a diagnostic test would be a liver biopsy or liver imaging (ultrasound, CT, MRI).

Screening programmes can be extremely successful. In the UK, screening programmes operate for some cancers, hereditary genetic diseases and other conditions such as abdominal aortic aneurysm and diabetic retinopathy. However, there are inherent costs and harms associated with screening. There are ethical, economic, social and legal arguments which must be carefully considered. In 1968 Wilson and Jungner, for the World Health Organisation, proposed criteria for deciding whether screening was appropriate.[51] These principles are still used today, they are listed below,[52] with comments pertaining to the context of liver disease:

1. **The disease should be an important health problem**
   The precise definition of 'importance' could be argued, but liver disease stands out as the majority of mortality is in working age people. Liver disease accounted for 1.25 million deaths in 2016 (2.3% of the global average).[53] Incidence and prevalence of liver disease are also increasing.

2. **There should be an accepted treatment for patients with recognised disease**
   For liver fibrosis stage F1 or F2, disease is reversible and could potentially be 'cured' by behaviour changes. For liver fibrosis stage F3 and cirrhosis (F4), it is currently not thought possible to reverse disease, but progression may be halted. Treatment of complications such as varices is also beneficial.

3. **Facilities for diagnosis and treatment should be available**
   Hepatologists in secondary care work either as a separate specialty, or within gastroenterology. The current model is a 'spoke and hub' approach. Every hospital has some provision (spokes), some are specialist tertiary referral centres for hepatology (hubs). Diagnosis facilities will depend on the method used. Liver biopsy can only be performed in hospital, whereas Fibroscan® can be performed in any community setting

including primary care. If screening were to detect a large number of cases, as has been suggested,[54] facilities would need to be scaled up in both primary and secondary care.

4. **There should be a recognisable latent or early symptomatic stage**

   Liver disease has a considerable latent phase, where signs and symptoms do not manifest but disease can still be detected.

5. **There should be a suitable test or examination**

   Some of the available tests have been discussed in section 1.4 and the suitability of these tests is discussed further in chapter three and chapter five. This is probably the weakest point of the argument for screening for liver disease.

6. **The test should be acceptable to the population**

   Non-invasive blood tests and transient elastography are both deemed acceptable to the population.

7. **The natural history of the condition should be understood**

   There is clear progression from F1 through to F4 (cirrhosis) (Figure 4). Research in to whether F3/4 disease is reversible continues currently.

8. **There should be an agreed policy on whom to treat as patients**

   Liver disease, as with any disease, exists in a spectrum within the population. At the more severe end of the spectrum, cases are clear. At the less severe end, for example F1, clear criteria need to be set to determine who should be treated. Treatment at this end of the spectrum is likely to differ greatly from that at the severe end of the spectrum, as the disease has the potential to be reversed. Should a 'case' be defined as someone with more advanced fibrosis? Not enough is currently known about the people in whom disease advances more rapidly, compared to those in whom it remains relatively stable.

9. **The cost of case finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole**

   There is an opportunity cost associated with any healthcare programme, in a landscape of limited resources. A health economic analysis would need to demonstrate that screening for liver disease would be cost-effective, providing good value for money for the NHS and patients.

10. **Case finding should be a continuing process and not a 'once and for all' project**

Incidence of liver disease is increasing and therefore case finding would need to be a continuous process.

These criteria have evolved over the past 40 years, as knowledge has advanced and particularly in the light of genetics and the possibility of genetic screening.[55] One important addition is the point that 'the overall benefits of screening should outweigh the harm'.[55]

As can be seen from these criteria, before a screening programme for chronic liver disease could be considered, a more reliable 'screening test' needs to be determined. This could be as single test, a combination of tests, or a combination of risk factors and tests. No screening test is perfect and there will always be some false negatives, or false positives, that arise. There are considerable harms associated with these – from unnecessary invasive testing and anxiety in false positives, to delayed treatment seeking and mistaken reassurance in false negatives. The sensitivity and specificity of currently available tests needs to be established in the general population setting in order to assess their validity for use in screening. Communication of the benefits and risks of participating in screening, and the consequences of participation, is extremely difficult.

In addition, before considering a screening programme a full cost effectiveness analysis would need to be undertaken. This would include assessments of the cost of screening, associated diagnostic tests and treatment, and the cost of not detecting early disease in terms of treating severely unwell patients with advanced disease. Primary prevention is usually considered to be more cost effective than screening programmes.[43] However, as liver disease has a long natural history, the benefit in improved outcomes for those detected with early disease may be decades ahead.

A common criticism of screening is that it does not change the ultimate clinical course of disease, it just makes people aware of their diagnosis earlier, and so they appear to survive longer. This is called lead-time bias. In the case of liver disease, there is a strong argument for the benefit of detecting disease earlier in the clinical course, whilst it is still reversible. Another potential pitfall is widening of health inequalities, since uptake of screening is lower in the most deprived. In the case of liver disease (as with many others) the most deprived are the most at risk, so it would be vital to ensure high uptake in this group.

At the moment, there is not a sufficiently strong evidence base for screening for chronic liver disease. A case finding approach could also be considered. This involves active, systematic searching for people at high risk of disease. There are similarities to screening. Both strategies involve population risk stratification to identify those at high risk. Both strategies seek to identify disease early, in order to improve outcomes.[43] Recent work to actively case find using a primary

care database in Basildon proved unsustainable, despite identifying many new cases. The process took too long and required repeatedly running the enquiry for the whole database (Sarah Fairclough, liver nurse at Basildon Hospital, oral presentation at BASL annual meeting 2019). This strategy may still be effective, with improvements in technology. However, the fundamental premise is that we understand the characteristics of those most at risk, so they can be identified and targeted. Adding to the evidence on who is most at risk, is a key part of the aims of this research.

1.9 Rationale for and aims of this research

Studies have estimated that the prevalence of liver fibrosis in the general population may range from 0.7% to 25.7%, with estimates of advanced fibrosis ranging from 0.9% to 2.0% (based on non-invasive markers).[54] Mortality is high in those who present with late disease. The desire is therefore to identify patients at risk of, or in the early stages of liver disease and to deliver interventions to change the clinical course, improving patient outcomes.

Reports from the All Party Parliamentary Hepatology Group and the Lancet Liver Commission have both emphasised the importance of primary care in identifying liver disease, and the need for improvements in this area.[2 56] Liver disease research has tended to focus on secondary care, treatments and management of severe disease. For liver disease prevention strategies to be successful, greater understanding is needed within the context of general population and community settings.

The overarching aim of this research was to increase the evidence base around prevention and early detection of liver disease in the general population setting. The specific objectives are described in the next section.

1.10 Research objectives

1. To explore the relationship between the combination of alcohol and BMI on risk of liver disease. To investigate whether there is an interaction between alcohol and BMI, on risk of chronic liver disease.
   Systematic review and meta-analysis of cohort studies. Chapter 2.

2. To obtain estimates of the risk of chronic liver disease associated with combinations of alcohol and BMI risk factors.
   Systematic review and meta-analysis of cohort studies. Chapter 2.

3. To explore risk factors for liver disease amongst the general population of England. To explore co-clustering of risk factors, and associations between risk factors and sociodemographic/socioeconomic variables.
   Analysis of the Health Survey for England. Chapter 3.

4. To explore the results of non-invasive tests for liver disease in the general population, by sociodemographic/socioeconomic variables and by risk factor categories.
   Analysis of the Health Survey for England. Chapter 3.

5. To describe the pattern of alcohol consumption and calories from alcohol, in those who are overweight or obese in a UK general population sample.
   Analysis of the National Diet and Nutrition Survey. Chapter 4.

6. To explore associations between sociodemographic variables, BMI and calories from alcohol.
   Analysis of the National Diet and Nutrition Survey. Chapter 4.

Chapter 2: The combined effect of alcohol and increased BMI on risk of chronic liver disease: a systematic review and meta-analysis

2.1 Research objectives

1. To explore the relationship between alcohol and BMI on risk of liver disease. To investigate whether there is an interaction between alcohol and BMI, on risk of chronic liver disease.

2. To obtain estimates of the risk of chronic liver disease associated with combinations of alcohol and BMI risk factors.

2.2 Background

Alcohol consumption and obesity are two of the three main causes of liver disease.[2 5 57] The prevalence of obesity continues to rise, with associated Non-Alcoholic Fatty Liver Disease (NAFLD) now affecting one in four people in Western countries.[6 7] Alcohol related liver disease is estimated to cause 60% of all liver disease in the UK. Clustering of unhealthy behaviours is common[48] and the health of many patients is adversely affected by the dual risks of alcohol and obesity, yet the interplay of these risk factors is not well understood.

Evidence from individual studies on the extent of the increased risk of liver disease associated with a combination of obesity and alcohol risk factors has been inconsistent, with varying estimates of risk.[58-60] Several studies have focused on the risks of alcohol consumption in patients with existing NAFLD, but there is little information in the general population setting. The most widely quoted paper on this subject, by Hart et al. in 2010,[59] suggested an interaction between alcohol and obesity in relation to the risk of liver disease. They found that obese men drinking more than 15 units of alcohol per week were nearly 19 times more likely to die from liver disease, compared to normal or underweight men who did not drink any alcohol. However, the true risk could have been anywhere between seven and 52 times greater. This large variation in the estimate of risk is because the sample size was relatively small, under 10,000 men, and liver disease deaths are a relatively infrequent occurrence. In addition, this study only included men and they were all from Scotland which has a higher percentage of deaths from liver disease than the rest of the UK. These results may therefore not be representative of the situation in the general population.

In order to succeed in primary prevention of liver disease, patients need to understand their personal risk profile. They are presented with conflicting evidence about reduced cardiovascular mortality associated with light to moderate alcohol consumption, but detrimental effects of alcohol associated with liver disease, some cancers and other chronic diseases.[61-64] Knowledge of the aetiology of liver disease is known to be low in the general population[46] and this must improve, so that people can make informed choices about their health.

Accurately quantifying risk is important, in order to communicate it effectively.[65] This will help patients make informed choices about lifestyle risk factors; it will support healthcare professionals in giving accurate information to their patients, risk stratifying them appropriately, and differentiating who would benefit from further testing; it will facilitate clinical referral pathways; it will help policy makers to target interventions and advice appropriately.

2.3 Methods

The protocol for this systematic review and meta-analysis was registered in advance with PROSPERO (International Prospective Register of Systematic Reviews, no. CRD42016046508). Covidence (www.covidence.org) was used by the review team for all stages of the review process.[66] Ethical approval for this work was granted by the University of Southampton Research Ethics Committee (ID: 19594).

2.3.1 Search strategy

We performed electronic searches of Ovid medline from 1946 and Embase Classic + Embase from 1947, until 18th February 2019. We manually searched clinical guidelines and reference lists of all included papers for other relevant research. Searches were limited to humans and papers not in English language were translated. Study authors were contacted where required. Search terms for liver disease were combined alternately with search terms for alcohol and obesity/BMI. Search terms are described in full in Table 4.

Table 4: Search terms used

Liver disease terms	1. *cholestasis, intrahepatic/ or *fatty liver/ or *fatty liver, alcoholic/ or *non-alcoholic fatty liver disease/ or *liver failure/ or *end stage liver disease/ or *hepatic encephalopathy/ or *liver failure, acute/ or *acute-on-chronic liver failure/ or *hepatitis, alcoholic/ or *hepatorenal syndrome/ or *hypertension, portal/ or *"esophageal and gastric varices"/ or *liver cirrhosis/ or *liver cirrhosis, alcoholic/ or *liver diseases, alcoholic/ or *carcinoma, hepatocellular/ 2. Liver Diseases/ep, et, mo [Epidemiology, Etiology, Mortality] 3. Liver Cirrhosis/ep, et, mo [Epidemiology, Etiology, Mortality] 4. 1 or 2 or 3 5. limit 4 to (humans)
Liver disease terms were combined in turn with each of the following sets of search terms:	
Obesity / BMI terms:	1. Obesity/ep, et, mo [Epidemiology, Etiology, Mortality] 2. Overweight/ep, et, mo [Epidemiology, Etiology, Mortality] 3. *body mass index/ 4. 1 or 2 or 3 5. limit 4 to (humans)
Alcohol terms	1. Alcohol Drinking/ 2. limit 1 to (humans)

2.3.2 Study selection

Citations and abstracts were imported in to Covidence (www.covidence.org).[66] Covidence detected duplicates, which were checked by one reviewer (KGO). At each stage of the review process, two team members (KGO and RB) independently reviewed the studies. In cases of disagreement, the papers were discussed with neither reviewer aware of what their initial decision had been. If agreement could not be reached, a third reviewer (JP) would have made the final decision but this was not necessary.

Studies were initially screened by title and abstract, and then by full text, to determine which studies met the a priori selection criteria. We considered all cohort studies with outcome data on incidence of or mortality due to liver cirrhosis, which also included quantifiable data on participants' alcohol consumption and BMI. We included studies if BMI or alcohol consumption had been measured, but data were not presented in the published paper. Where eligible studies had not presented data on BMI or alcohol consumption, or data were not in the required format for the meta-analysis, we contacted authors directly, via email, to request data. All authors were emailed a second time if no response had been received from the first contact. Where data from the same cohort was used for more than one published study that met the eligibility criteria, only one study was included, as per protocol.

2.3.3 Inclusion criteria

Criteria for studies included in the review were described using the PICOS criteria and are shown in Table 5. Briefly, inclusion criteria were: cohort studies of adults without pre-existing liver disease, where data were collected on BMI and a quantifiable measure of alcohol consumption. Outcomes were risk of incident morbidity or mortality due to liver cirrhosis.

Studies that only involved participants with a specific liver or non-liver disease were excluded e.g. cohort of diabetes patients, cohort of patients with viral hepatitis, liver transplant patients. Studies that did not adjust for the effects of Hepatitis B (HBV) or Hepatitis C (HCV) and were conducted in areas with a high (>2%) background prevalence of HBV or HCV (from published epidemiological data available in January 2019) were also excluded. If data from the same cohort were used for more than one published study, only the study deemed by the reviewers to be of the highest quality, with the most comprehensive population and estimates of risk was included.

Table 5: Criteria for including studies in the review

Population/participants	Adults aged 18 years or over, without pre-existing liver disease
Interventions or exposures	Overweight/obesity measured as BMI Alcohol consumption, quantifiably measured
Comparisons or control groups	Adults aged 18 years or older, with information about BMI and alcohol consumption, who did not develop liver cirrhosis
Outcomes of interest	Incident morbidity or mortality due to liver cirrhosis. Diagnosis to be confirmed by any of: appropriate diagnostic imaging, histology, cancer registry, ICD code, clinician's diagnosis
Setting	General population setting
Study design	Cohort studies only

After full text review, all studies which met the inclusion criteria were further assessed, to ascertain whether the data required for the meta-analysis were presented in the published paper or not. Where data were not presented, authors were contacted in order to request the required data.

2.3.4 Data extraction and risk of bias assessment

For each study included in the meta-analysis, one review team member (KGO) extracted the data using a standardised template. A second team member (RB) checked the data extraction. Any inconsistencies were resolved through discussion, with a third review team member (JP) ready to arbitrate but this was not necessary. Data collected were:

a) General study information (authors, year, country, study design, enrolment period, inclusion and exclusion criteria, measures to reduce bias, and funding source)

b) Study population details (sample and setting, participants, age, sex)

c) Exposure details (Alcohol measurement method and how recorded; BMI measurement method and how recorded; measurement of or measures taken to account for viral hepatitis)

d) Outcome details (outcome measures collected, method of ascertainment, steps taken to ensure outcome measure not present at baseline, method of follow-up, duration of follow-up, and loss to follow-up)

Quality assessment and risk of bias was assessed using the Newcastle-Ottawa Scale (NOS) for quality assessment of cohort studies,[67] using information presented in the published study and/or published protocols and methods. The criterion for adequacy of follow-up was set as at least ten years. Included studies were assessed independently by two reviewers. A third reviewer would have had the final decision if agreement could not be reached.

2.3.5 Data preparation

The available data and/or extra data where provided by authors, were used to cross tabulate numbers of participants in nine categories of BMI and alcohol consumption. BMI categories were normal (<25 kg/m^2), overweight (≥25 to <30 kg/m^2) and obese (≥30 kg/m^2) and were not ethnicity-specific. Alcohol categories were none, within recommended limits (>0 to 14 units/112 grams per week) and above recommended limits (>14 units/112 grams per week).[68] Alcohol data were provided in a variety of formats, with measures in 'drinks', grams and UK units. Table 6 shows how these data were re-categorised in to the alcohol categories described above.

Table 6: Details of how alcohol consumption categories were re-categorised in order to make them comparable

Author and study year	Alcohol categories used or provided by authors	Re-categorised	Equivalent in grams*
Aberg 2018	0 units/week 1-14 units/week ≥15 units/week	no	0 g/day >0 to 16g/day ≥17g/day
Hart 2010	0 units/week 1-14 units/week ≥15 units/week	no	0 g/day >0 to 16g/day ≥17g/day
Liu 2010	1 to <150 g/week ≥150 grams/week	1-14 units/week ≥15 units/week	>0 to 16g/day ≥17g/day
Persson 2013	0 drinks/day <1 drink/day 1-3 drinks/day >3 drinks/day	0 drinks/day <1 drink/day >1 drink/day	0 g/day >0 to <16g/day >16g/day
Schult 2018	None 1-16g/day >16g/day	no	0 g/day 1-16g/day >16g/day
Schwartz 2013	0 g/day >0 - <17g/day ≥17g/day	no	0 g/day >0 to <17g/day >17g/day
Setiawan 2018	0 drinks/day <2 drinks/day ≥2 drinks/day	no	0 g/day >0 to <32g/day ≥32g/day
Trembling 2017	0 units/week <1 – 15 units/week 16 – 20 units/week ≥ 21 units/week	0 units/week <1 – 15 units/week ≥ 16 units/week	0 g/day >0 to 17g/day ≥17 g/day
* assuming 1 drink = 2 units = 16 grams alcohol			

The numbers of cases and the total number of exposed participants in each category were also entered. Where individual study data could not be reasonably re-categorised in to these categories, and the required data were not available from the authors, the study was excluded.

2.3.6 Statistical analysis

2.3.6.1 Log linear model

A Poisson regression, log linear model, was used to generate coefficients for each category of BMI and alcohol against the reference categories, which were normal weight (BMI<25 kg/m^2) and within limits alcohol consumption (>0 to 14 units (112g)/wk). The model used random effects to account for baseline study heterogeneity and a fixed parameter to estimate the exposure effect. The log-linear model relates the logarithmic count of cases with the factors alcohol consumption and BMI, where:

- count ijk are the number of cases in study i, alcohol category j and BMI category k
- n ijk are the number at risk in study i, alcohol category j and BMI category k
- alc j is the log relative risk (RR) for alcohol
- bmi k is the log RR for BMI
- alc#bmi jk is the potential interaction

Equation 1

$$\log(\text{count}\ ijk) = \text{study}i + \text{alc}j + \text{bmi}k + (\text{alc\#bmi})jk + \log(\text{n}ijk)$$

Even in the absence of the interaction term $(\text{alc\#bmi})jk$ the effects of alcohol consumption and BMI work multiplicatively. This is because, without the interaction term, Equation 1 is equivalent to:

Equation 2

$$\text{count}\ ijk / \text{n}\ ijk = \exp(\text{study}\ i) \times \exp(\text{alc}\ j) \times \exp(\text{bmi}\ k).$$

For example, if the single effect of alcohol above limits is three and the single effect of obesity is three, then the joint effect is nine (and not six as it would be in an additive model).

The reference group was chosen as participants consuming within UK recommended limits of alcohol consumption (≤14 units/week[68]), rather than zero alcohol consumption, due to the heterogeneity often described in those who report zero alcohol consumption (including many ex-drinkers or those who have given up alcohol due to ill health).[69 70] Study and sample size were entered in to the model to avoid any confounding effects. The model was run with and without an interaction term for BMI and alcohol.

Relative risks were then calculated from the exponential of the coefficients.
For individual categories, RR = exp (coefficient).

For combinations of categories, RR = exp (coefficient category A + coefficient category B).

2.3.6.2 Sensitivity analysis

Sensitivity analyses (not pre-specified) were performed, to check for any undue effects from the following:

1. excluding data from the paper (Setiawan 2018) in which the alcohol consumption data was most different to the categories used in the meta-analysis
2. excluding data from the paper (Persson 2013) which was rated 'poor' in quality assessment
3. excluding the data from Liu 2010, which did not include any information about people who reported zero alcohol consumption
4. excluding all data on participants who reported zero alcohol consumption. This group are known to be highly heterogeneous and may contain many ex-drinkers which might bias the data.

2.3.6.3 Meta-analysis

Data were used from all studies for which adequate data were available. The relative risk of cirrhosis in different BMI and alcohol consumption categories, and combinations of categories, was calculated. As original count data were available for included studies, a direct approach was used to perform a one-stage meta-analysis, estimating the relative risk from each study individually and for all studies combined. This is in contrast to the two-stage analysis, which is used where only summary statistics are available. Advantages of the one-stage analysis include the fact that it does not assume a normal distribution; original count data can be utilised and the issue of summary statistics from different studies being adjusted for different variables does not arise. The one-stage model gives a more robust estimate of risk. However, it should be noted that the analysis is not adjusted for anything other than the variables in the model (for example there is no age or sex adjustment possible).

The reference group for the meta-analysis was participants of normal weight and drinking within recommended limits of alcohol. The zero alcohol group was not used, due to the known heterogeneity of this group. Other studies have shown that the zero alcohol group includes a large number of previously alcohol-dependent participants.[69] This may bias the results, as their

risk of cirrhosis would be considerably higher than someone who had never consumed any alcohol. Zero alcohol data were also not available for one study.

Publication bias, small study effects and heterogeneity were assessed using visual inspection of funnel plots and appropriate statistical tests.[71 72]

2.3.6.4 Sub-group analysis

A sub-group analysis was performed in the one study which allowed for separation between intermediate risk and higher risk alcohol consumption. The same methods used in the main analysis were used to investigate the effects of overweight and obesity combined with intermediate risk or high risk alcohol consumption.

Data were analysed using STATA version 14·2.

2.4 Results

2.4.1 Search results

The initial search returned 2,904 papers, of which 389 were duplicates. 2,451 records were excluded by review of title and/or abstract. Full text review of 64 papers was conducted and 49 were excluded. Study selection is shown in Figure 10. In total, 15 studies met the eligibility criteria. From these, data were available or provided by authors for eight studies, which were included in the meta-analysis.

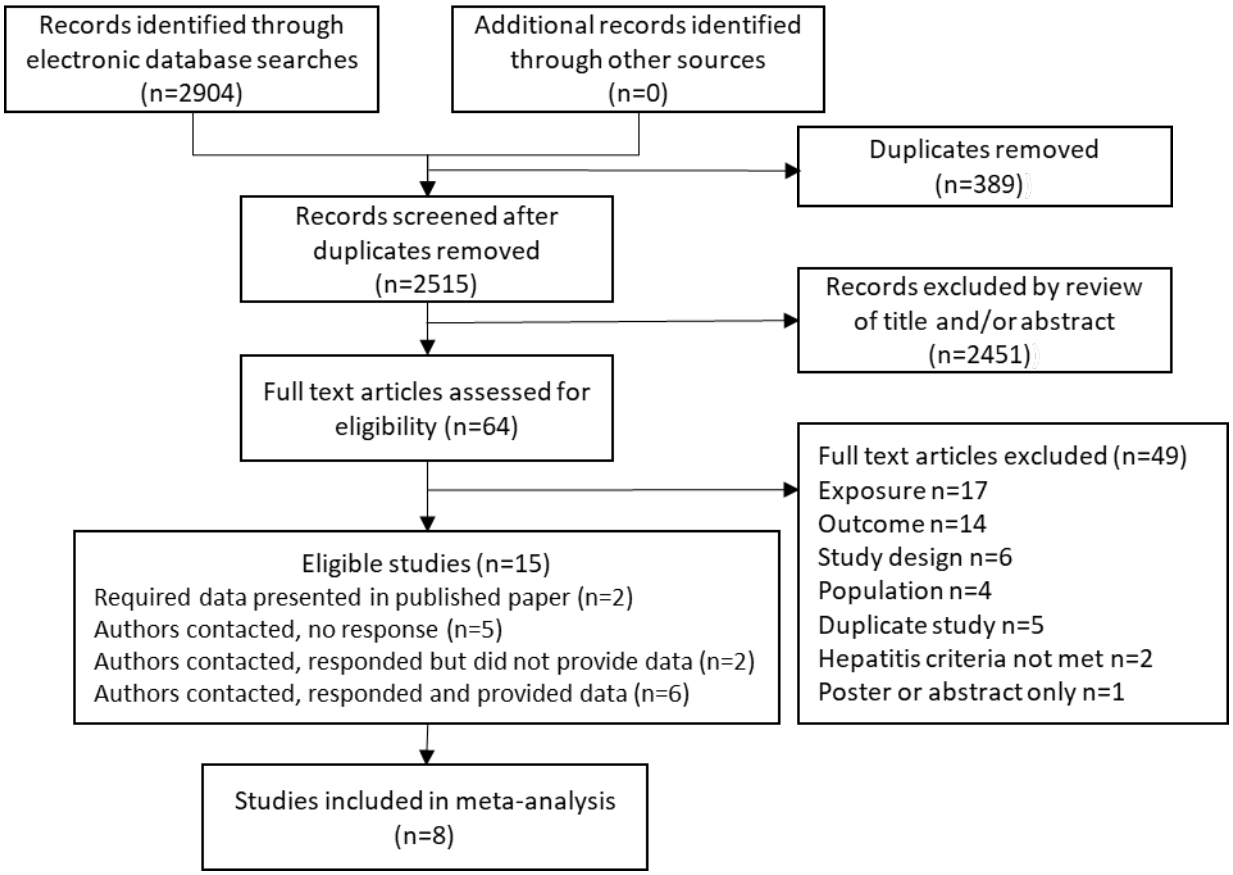


Figure 11: PRISMA flow diagram

2.4.2 Eligible studies

The eight studies included in the meta-analysis are summarised in Table 7 and Table 8. They included 1,029,962 participants, from eight cohorts - six European cohorts and two from the USA. All studies had recorded cases of cirrhosis, measured either as hospitalisation with, or mortality from cirrhosis. All but one study included measurement of cases of Hepatocellular Carcinoma (HCC). This was measured as either incidence of, or mortality from HCC. Cirrhosis was the primary outcome measure, however HCC is a known sequela of cirrhosis. HCC cases were therefore included where provided. Many of the eligible studies reported cases of 'chronic liver disease', which included cirrhosis and/or HCC and/or other ICD codes deemed to represent liver cirrhosis. The terminology 'chronic liver disease' is therefore used to reflect this.

Prevalence of exposures varied between studies. Prevalence of obesity ranged from 5·5% to 25·1% and alcohol consumption above recommended limits ranged from 4·5% to 38·0%. Absolute risk of chronic liver disease in the reference group (normal weight and drinking within limits alcohol consumption), ranged from 0.11% to 0.90%. Absolute risk of chronic liver disease in the group at highest risk (obese and drinking alcohol above recommended limits) ranged from 0.58% to 7.83% over the follow-up periods of the studies.

Count data provided by authors have not been reproduced here, as permission to do so has not been granted by the original authors. The seven studies not included in the meta-analysis are summarised in Appendix A, Table 35 and Table 36.

Table 7: Baseline data for the eight cohort studies which were included in the meta-analysis

Author	Year	Country	Sample & setting	Participants	Gender	Age	Ethnicity	Follow up duration‡	Follow up method
Aberg[73]	2018	Finland	General population cohort.	6519	44% men	≥30yrs Mean 54yrs.	No information.	Mean 11·4yrs (SD 3·3yrs)	National Hospital Discharge Register, Finnish Cancer Registry and Statistics Finland databases.
Hart[59]	2010	UK	Working population cohort.	9559	Men only	Range 14-92yrs.	No information.	Median 29yrs.	NHS Central Register and Scottish Morbidity Records data.
Liu† [74]	2010	UK	Middle-aged women in England and Scotland.	376,164	Women only	50-64yrs. Mean age 56yrs	No information.	Mean 6.2yrs.	NHS health records for data on hospital admissions, deaths, cancer diagnoses and emigration.
Persson[75]	2013	USA	American Association of Retired Persons (AARP) members	477,178	59% men	50 to 71 yrs	Majority were white, non-Hispanic (91%).	Median 10·5yrs.	State cancer registries (HCC). US Social Security Administration Death Master File and National Death Index Plus.
Schult[76]	2018	Sweden	General population sample.	1458	Women only	38-60yrs Mean 46·5yrs.	No information.	33yrs§	Hospital Discharge Registry and Central Bureau of Statistics.
Schwartz[77]	2013	Finland	General population sample of smokers.	27,094	Men only	50-69yrs	No information.	22·5yrs§	Finnish Cancer Registry. Finnish Register of Causes of Death.
Setiawan[78]	2016	USA	General population cohort.	36,864	50% men	45-75yrs	Hispanic and Latino only.	Median 19·6yrs.	Cancer surveillance program for Los Angeles County. California State Cancer Registry. Linkage to state death certificates in California and the National Death Index.
Trembling[79]	2017	UK	Post-menopausal women living in England.	95,126	Women only	50-74yrs	No information.	5·1yrs§	NHS information centre for health and social care in England and Wales. HES data linkage 2001-10. Death certificate data.

† A paper published by Liu et al in 2009 also met the eligibility criteria but the data were from the same cohort of women as the 2010 paper. As per protocol, to avoid duplication of data, we assessed both papers and the 2010 paper only was included in the review and meta-analysis.

‡ Median or mean follow-up duration if stated. If not stated, calculated depending on available information as a) mid-point of possible range of follow-up durations or b) total person years of follow-up time divided by number of participants.

§ Indicates that follow-up duration has been calculated.

UK – United Kingdom, USA – United States of America, SD – Standard Deviation, HCC – Hepatocellular carcinoma, HES – Hospital Episode Statistics.

Table 8: Exposure and outcome summary data for the eight cohort studies which were included in the meta-analysis

Author	Year	Total cases	Outcome	BMI assessment	BMI<25	BMI 25 to <30	BMI≥30	Alcohol assessment	Alcohol zero	Alcohol within UK limits‡ >0 to 14 units/wk	Alcohol above UK limits‡ ≥15 units/wk
Aberg[73]	2018	84 (1·3%)	CLD hospitalisation or mortality HCC incidence	Measured	37·7%	39·9%	22·4%	Self-reported	35·4%	45·3%	19·3%
Hart[59]	2010	146 (1·5%)	CLD mortality HCC mortality	Main study: self-reported Collaborative study: measured	52·7%	41·9%	5·5%	Self-reported	35·1%	37·5%	27·4%
Liu† [74]	2010	1443 (0·4%)	Cirrhosis hospitalisation or mortality	Self-reported	50·0%	37·1%	13·0%	Self-reported	0·0%	90·5%	9·5%
Persson[75]	2013	1165 (0·2%)	CLD mortality HCC incidence	Self-reported	35·4%	42·9%	21·7%	Self-reported	23·8%	53·1% <1 drink/day	23·1% ≥1 drink/day
Schult[76]	2018	11 (0·8%)	Cirrhosis hospitalisation or mortality HCC hospitalisation or mortality	Measured	66·8%	25·6%	7·6%	Structured interview	24·5%	63·0% 1-16g/day	12·5% >16g/day
Schwartz[77]	2013	410 (1·5%)	CLD mortality HCC incidence	Measured	38·5%	46·3%	15·2%	Food frequency questionnaire	11·2%	50·9% <1 drink/day	38·0% ≥1 drink/day
Setiawan[78]	2016	487 (1·3%)	CLD mortality HCC incidence	Self-reported	28·0%	46·9%	25·1%	Food frequency questionnaire	49·9%	41·0% <2 drinks/day	9·1% ≥2 drinks/day
Trembling[79]	2017	325 (0·3%)	CLD incidence HCC incidence	Self-reported	44·6%	36·9%	18·5%	Self-reported	23·4%	72·1% >0 to 15 units/wk	4·5% ≥16 units/wk

† A paper published by Liu et al in 2009 also met the eligibility criteria but the data were from the same cohort of women as the 2010 paper. As per protocol, to avoid duplication of data, we assessed both papers and the 2010 paper only was included in the review and meta-analysis.
‡ Assumes 1 drink = 2 units = 16 grams of alcohol
HCC – Hepatocellular Carcinoma, CLD – Chronic Liver Disease (including cirrhosis), BMI – Body Mass Index

2.4.3 Quality assessment and risk of bias

Assessment of quality and risk of bias for all studies included in the meta-analysis was performed using the Newcastle-Ottawa criteria for cohort studies. The full assessment criteria used are detailed in Appendix A. Criteria are also provided for converting the Newcastle-Ottawa scales to AHRQ standards, as follows:

Good quality: Three or four stars in selection domain and one or two stars in comparability domain and two or three stars in outcome/exposure domain

Fair quality: Two stars in selection domain and one or two stars in comparability domain and two or three stars in outcome/exposure domain

Poor quality: Zero or one star in selection domain or zero stars in comparability domain or zero or one stars in outcome/exposure domain

Results are shown in Table 9. Overall five studies were rated 'good', two were 'fair' and one was 'poor'.

Table 9: Quality assessment and risk of bias for all studies included in the meta-analysis, using the Newcastle Ottawa criteria for cohort studies.

Author	Year	Selection				Comparability	Outcome			Interpretation
		1	2	3 BMI/alcohol	4	1	1	2	3	
Aberg[73]	2018	*	*	*/0	*	**	*	*	*	Good
Hart[59]	2010	*	*	0/0	*	**	*	*	0	Good
Liu[74]	2010	*	*	0/0	*	**	*	0	*	Good
Persson[75]	2013	0	*	0/0	0	**	*	*	0	Poor
Schult[76]	2018	*	*	*/*	0	*	*	*	*	Good
Schwartz[77]	2013	0	*	*/0	*	**	*	*	*	Good
Setiawan[78]	2016	*	*	0/0	0	**	*	*	0	Fair
Trembling[79]	2017	*	*	0/0	0	*	*	0	*	Fair

Selection
1. Representativeness of the exposed cohort
2. Selection of the non-exposed cohort
3. Ascertainment of exposure
4. Demonstration that outcome of interest was not present at start of study

Comparability
1. Comparability of cohorts on the basis of the design or analysis

Outcome
1. Assessment of outcome
2. Was follow-up long enough for outcome to occur
3. Adequacy of follow up of cohorts

2.4.4 Findings from eligible studies

As can be seen in Figure 10, although 15 studies met the eligibility criteria, only eight studies were able to provide the data required for meta-analysis. A brief summary of findings from all 15 eligible studies is included here:

Five of the 15 eligible studies reported on the combined effects of alcohol and obesity on risk of liver disease, and three made an assessment of interaction between BMI and alcohol consumption. One study[79] reported no significant interaction, whereas another[80] reported a significant ($p<0.05$) interaction between alcohol consumption and BMI categories. A third study[59] calculated a 'Relative Excess Risk of Interaction (RERI)' of 5·58 due to the interaction of high BMI and high alcohol consumption. Two studies[74 80] investigated trends in risk of liver disease, among

alcohol consumers, across BMI categories and found no statistically significant associations, suggesting no statistical interaction.

Relative risks of liver disease among different combinations of alcohol and BMI categories varied across studies. For participants drinking higher amounts of alcohol, if also obese relative risks were 2·86 (≥21 units/week),[79] 4·06 (≥210g/week men, ≥140g/week women),[73] 6·53 (≥150g/week),[74] and 9·73 (≥15 units/week).[59] For participants drinking higher amounts of alcohol, if also overweight the relative risk was 3·32 (≥21 units/week).[79] For participants consuming some, but lower quantities of alcohol, relative risks if also obese were 1·48 (<210g/week for men, <140g/week for women),[73] 2·31 (70 to <150g/week),[74] and 4·50 (1-14 units/week).[59]

2.4.5 Poisson regression results

The Poisson model showed no significant statistical interaction between combinations of alcohol consumption and BMI, on risk of chronic liver disease. The model was run for each study individually, and for all studies combined in a random effects summary analysis (Table 10). The coefficient indicates that the difference in the logs of expected counts of cases (of CLD) is expected to change by a factor of [coefficient value] for each category, when compared to the reference category.

Table 10: Poisson regression model for interaction of BMI and alcohol, for all eight studies combined

		Coefficient	P value	95% confidence intervals	
BMI # Alcohol interaction	**Normal weight Within limits alcohol**	Ref			
	Overweight No alcohol	-0.12	0.267	-0.33	0.09
	Obese No alcohol	-0.16	0.154	-0.37	0.06
	Overweight Above limits alcohol	-0.02	0.779	-0.18	0.14
	Obese Above limits alcohol	-0.16	0.086	-0.35	0.02

The AIC and BIC for the model were lower when interaction was removed, confirming that the model was a better fit without interaction. However, the risks of BMI and alcohol consumption are multiplicative, as per the properties of the log linear model.

The model is therefore run without an interaction term (Table 11). The Poisson regression model also allows results to be expressed as incidence rate ratios, which are more intuitive to interpret (Table 12).

Table 11: Poisson regression model for all studies individually, and all studies combined

	BMI			Alcohol		
	Normal weight	**Overweight Coefficient (95%CIs)**	**Obese Coefficient (95%CIs)**	**Within limits**	**Zero alcohol Coefficient (95%CIs)**	**Above limits Coefficient (95%CIs)**
Aberg 2018	Ref	0.03 (-0.48, 0.54)	0.36 (-0.19, 0.91)	Ref	0.40 (-0.19, 1.00)	1.54 (1.00, 2.08)
Hart 2010	Ref	0.53 (0.17, 0.88)	1.10 (0.56, 1.63)	Ref	-0.70 (-1.25, -0.15)	1.06 (0.68, 1.43)
Liu 2010 ‡	Ref	0.24 (0.13, 0.36)	0.83 (0.70, 0.97)	Ref	n/a	1.13 (1.01, 1.25)
Persson 2013	Ref	0.14 (-0.00, 0.28)	0.59 (0.44, 0.74)	Ref	0.65 (0.51, 0.80)	1.03 (0.89, 1.16)
Schult 2018†	Ref	0.82 (-0.37, 2.01)	n/a	Ref	-0.83 (-2.95, 1.29)	1.18 (-0.09, 2.44)
Schwartz 2013	Ref	0.20 (-0.02, 0.43)	0.51 (0.24, 0.78)	Ref	-0.09 (-0.49, 0.32)	0.83 (0.62, 1.03)
Setiawan 2018	Ref	0.17 (-0.07, 0.40)	0.65 (0.41, 0.90)	Ref	0.17 (-0.03, 0.38)	1.15 (0.90, 1.39)
Trembling 2017	Ref	0.37 (0.11, 0.63)	0.83 (0.55, 1.11)	Ref	0.36 (0.12, 0.60)	0.58 (0.14, 1.02)
All studies combined	Ref	0.23 (0.16, 0.30)	0.71 (0.63, 0.80)	Ref	0.37 (0.27, 0.46)	1.05 (0.98, 1.13)

† The Schult data contained no cases who were obese.

‡ The Liu data provided did not include any information about participants who reported drinking zero alcohol.

Table 12: Poisson regression model results, showing incidence rate ratio of chronic liver disease in participants with varying BMI and alcohol consumption

	BMI			Alcohol		
	Normal weight	**Overweight Incidence Rate Ratio (95%CIs)**	**Obese Incidence Rate Ratio (95%CIs)**	**Within limits**	**Zero alcohol Incidence Rate Ratio (95%CIs)**	**Above limits Incidence Rate Ratio (95%CIs)**
Aberg 2018	Ref	1.03 (0.62, 1.72)	1.43 (0.82, 2.48)	Ref	1.49 (0.82, 2.71)	4.68 (2.73, 8.01)
Hart 2010	Ref	1.69 (1.19, 2.40)	2.99 (1.76, 5.11)	Ref	0.50 (0.29, 0.86)	2.88 (1.98, 4.19)
Liu 2010 ‡	Ref	1.28 (1.13, 1.44)	2.30 (2.01, 2.63)	Ref	n/a	3.10 (2.75, 3.50)
Persson 2013	Ref	1.15 (1.00, 1.32)	1.81 (1.56, 2.10)	Ref	1.92 (1.66, 2.23)	2.79 (2.43, 3.20)
Schult 2018†	Ref	2.27 (0.69, 7.45)	n/a	Ref	0.44 (0.05, 3.64)	3.25 (0.92, 11.50)
Schwartz 2013	Ref	1.23 (0.98, 1.53)	1.67 (1.27, 2.19)	Ref	0.92 (0.61, 1.37)	2.28 (1.85, 2.81)
Setiawan 2018	Ref	1.18 (0.93, 1.50)	1.92 (1.51, 2.45)	Ref	1.19 (0.97, 1.46)	3.15 (2.46, 4.03)
Trembling 2017	Ref	1.45 (1.11, 1.88)	2.29 (1.74, 3.03)	Ref	1.43 (1.13, 1.82)	1.79 (1.16, 2.79)
All studies combined	Ref	1.26 (1.17, 1.35)	2.04 (1.88, 2.21)	Ref	1.44 (1.31, 1.59)	2.86 (2.65, 3.08)

† The Schult data contained no cases who were obese.

‡ The Liu data provided did not include any information about participants who reported drinking zero alcohol.

For all studies combined, compared to normal weight participants, the incidence rate ratio of chronic liver disease in overweight participants was 1.26 (95%CI 1.17-1.35) and for obese participants it was 2.04 (95%CI 1.88-2.21). Compared to participants drinking alcohol within recommended limits, the incidence rate ratio of chronic liver disease in those drinking no alcohol was 1.44 (95%CI 1.31-1.59) and for participants drinking more than recommended limits it was 2.86 (95%CI 2.65-3.08) (Table 12).

The results of the specified sensitivity analyses are shown in Table 13. The greatest effect on the model was if data from the one study (Persson 2013[75]) which scored 'poor' on the quality assessment scale were removed (sensitivity analysis two). The effect of including this study was bidirectional: to increase the estimate of the risk of liver disease in overweight and obese, compared to normal weight participants; to increase the estimate of the risk of liver disease in participants consuming no alcohol, compared to those drinking within recommended limits; to decrease the estimate of the risk of liver disease in participants drinking above recommended limits of alcohol, compared to those drinking within recommended limits. After discussion with statistician colleagues, it was agreed that none of the sensitivity analyses showed effects which were compelling enough to require studies to be excluded from the final analysis.

Table 13: Poisson regression results for all studies, and for sensitivity analyses as detailed, expressed as incidence rate ratios

		All studies	Sensitivity analysis 1	Sensitivity analysis 2	Sensitivity analysis 3	Sensitivity analysis 4
		Incidence rate ratio (95% CIs)	Incidence rate ratio (95% CIs)	Incidence rate ratio (95% CIs)	Incidence rate ratio (95% CIs)	Incidence rate ratio (95% CIs)
BMI	Normal	Ref	Ref	Ref	Ref	Ref
	Overweight	1.26 (1.17, 1.35)	1.26 (1.17,1.37)	1.30 (1.19,1.42)	1.24 (1.13,1.36)	1.28 (1.18,1.39)
	Obese	2.04 (1.88, 2.21)	2.05 (1.88,2.24)	2.14 (1.94,2.35)	1.92 (1.73,2.13)	2.09 (1.91,2.29)
Alcohol consumption	Within limits alcohol	Ref	Ref	Ref	Ref	Ref
	No alcohol	1.44 (1.31, 1.59)	1.56 (1.40,1.73)	1.14 (1.00,1.29)	1.42 (1.28,1.57)	n/a
	Above limits alcohol	2.86 (2.65, 3.08)	2.85 (2.63,3.08)	2.94 (2.69,3.22)	2.73 (2.48,2.99)	2.85 (2.65, 3.08)

Sensitivity analyses:

1. Excluding data from Setiawan 2018, in which alcohol consumption data was most different to the categories used in the meta-analysis
2. Excluding data from Person 2013 which was rated 'poor' in quality assessment
3. Excluding data from Liu 2010, which did not include any information about participants who reported zero alcohol consumption
4. Excluding data on all participants who reported zero alcohol consumption.

As per the properties of the log-linear model, to assess the effect from combinations of alcohol and BMI categories, the relative risks for the individual effects were multiplied together (see methods). Hence:

RR(overweight and alcohol above limits) = RR(overweight)*RR(alcohol above limits)

RR(overweight and alcohol above limits) = 1.26 * 2.86 = 3.60.

This may also be expressed using the antilog of the sum of the log risks. The log risk is shown as the coefficient in the Poisson model output. So:

RR(overweight and alcohol above limits) = Exp [Log(RR overweight) + log(RR alcohol above limits)]

RR(overweight and alcohol above limits) = Exp [0.23 + 1.05] = 3.60.

Using this method, and the coefficients presented in Table 11, the combined risk of chronic liver disease for all combinations of alcohol consumption and BMI are presented in Table 14.

Table 14: Relative risk of chronic liver disease, for each study individually and all studies combined, in participants with differing combinations of alcohol consumption and BMI. Calculated using the results of the Poisson regression model.

	Normal weight and alcohol within recommended limits (<14 units/week)	Overweight and zero alcohol Relative Risk (95%CIs)	Obese and zero alcohol Relative Risk (95%CIs)	Overweight and alcohol above recommended limits (≥14 units/wk) Relative risk (95%CIs)	Obese and alcohol above recommended limits (≥14 units/wk) Relative risk (95%CIs)
Aberg 2018	Ref	1.54 (0.45, 5.30)	2.13 (0.74, 6.10)	4.82 (1.80, 12.92)	6.69 (2.21, 20.29)
Hart 2010 §	Ref	0.84 (0.36, 1.98)	n/a	4.87 (2.73, 8.68)	8.62 (4.17, 17.81)
Liu 2010 ‡	Ref	n/a	n/a	3.96 (3.11, 5.05)	7.12 (5.58, 9.09)
Persson 2013	Ref	2.21 (1.70, 2.88)	3.48 (2.65, 4.56)	3.20 (0.34, 30.17)	5.03 (3.82, 6.63)
Schult 2018 †	Ref	0.99 (0.10, 9.43)	n/a	7.37 (5.29, 10.26)	n/a
Schwartz 2013	Ref	1.12 (0.60, 2.10)	1.53 (0.55, 4.22)	2.80 (1.77, 4.42)	3.81 (2.61, 5.56)
Setiawan 2018	Ref	1.41 (0.92, 2.16)	2.29 (1.51, 3.47)	3.72 (3.06, 4.52)	6.06 (3.57, 10.27)
Trembling 2017	Ref	2.08 (1.39, 3.10)	3.28 (2.24, 4.80)	2.60 (1.34, 5.03)	4.11 (1.51, 11.22)
All studies combined	Ref	1.82 (1.58, 2.09)	2.95 (2.56, 3.39)	3.60 (3.22, 4.02)	5.84 (5.09, 6.70)

§ It was not possible to calculate relative risk of obese and zero alcohol from the Hart data, as there were no cases in this group

‡ It was not possible to calculate relative risk of zero alcohol from the Liu data, as no data on zero alcohol consumers was provided

† It was not possible to calculate relative risk of obesity from the Schult data, as there were no cases who were obese.

2.4.6 Sub-group analysis

Only one study had alcohol data in a form which allowed separation of 'above limits' alcohol consumption further, into intermediate risk and high risk alcohol consumption. For this study (Persson 2013) a sub-group analysis was performed, to look at the effects of overweight and obesity combined with intermediate risk or high risk alcohol consumption. The reference group was normal weight, within limits alcohol consumption (Less than one drink/day for this study). Intermediate risk was defined as one to three drinks/day. Assuming one drink is equivalent to two UK alcohol units, then this category included alcohol users consuming 14 – 42 units/week. High risk alcohol consumption was defined as more than three drinks/day or, using the same assumption, >42 units/week. Alcohol consumption is categorised by the National Institute for Health and Care Excellence (NICE) as 'harmful' if ≥35 units/week for women and ≥50 units/week for men.[81]

Using the Poisson regression model, and the same method previously described, the relative risks of chronic liver disease in this sub-group analysis are shown in Table 15. It should be noted that this study was the only study with a rating of 'poor' on the quality assessment scale. Both alcohol and BMI were self-reported. These findings should be viewed with caution, and further research to distinguish between intermediate and high risk alcohol consumers is needed before any conclusions can be made.

Table 15: Sub-group analysis. Relative risk of chronic liver disease in overweight/obese participants with intermediate risk or high risk alcohol consumption.

Persson et al. 2013	
BMI and alcohol consumption category	**Relative risk of chronic liver disease (95% CIs)**
Overweight + intermediate risk alcohol consumption	1.89 (1.41, 2.54)
Obese + intermediate risk alcohol consumption	2.94 (2.06, 4.20)
Overweight + high risk alcohol consumption	5.53 (4.23, 7.23)
Obese + high risk alcohol consumption	8.62 (6.26, 11.86)

2.4.7 Meta-analysis

The pooled relative risks for different combinations of BMI and alcohol consumption were combined using a meta-analysis and are illustrated in Figure 12 and Figure 14. The relative risk in those who were obese and drinking above limits alcohol (7 included studies), compared to normal weight and drinking within limits, was 5·84 (95%CI 5·09 to 6·70). Both Begg's (p= 0.881) and Egger's (p=0.810) tests were non-significant. On visual inspection the funnel plot (Figure 13) was symmetrical, indicating low chance of small study effects. The I^2 statistic was 40.7%, which may represent moderate heterogeneity.[82] It was not statistically significant (p=0.120).

The relative risk in those who were overweight and drinking above limits alcohol (8 included studies), compared to normal weight and drinking within limits, was 3.60 (95%CI 3.22 to 4.02). Both Begg's (p = 0.621) and Egger's (p = 0.745) tests were non-significant. On visual inspection the funnel plot (Figure 14) was symmetrical with one small study outlier, indicating low chance of small study effects. The I^2 statistic was 61.3% (p = 0.012), which may represent substantial heterogeneity.[82]

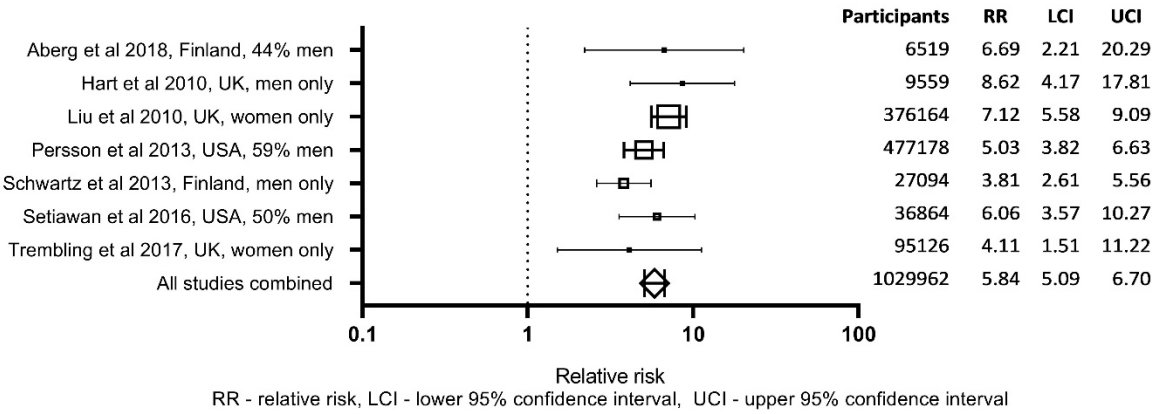


Figure 12: Relative risk (RR) of chronic liver disease in participants who are obese and drinking above recommended limits of alcohol (>14 units/week), compared to those who are normal weight and drinking within recommended limits (>0 ≤14 units/week). I-squared = 40.7%, p = 0.120. Box size indicates weight study contributes.

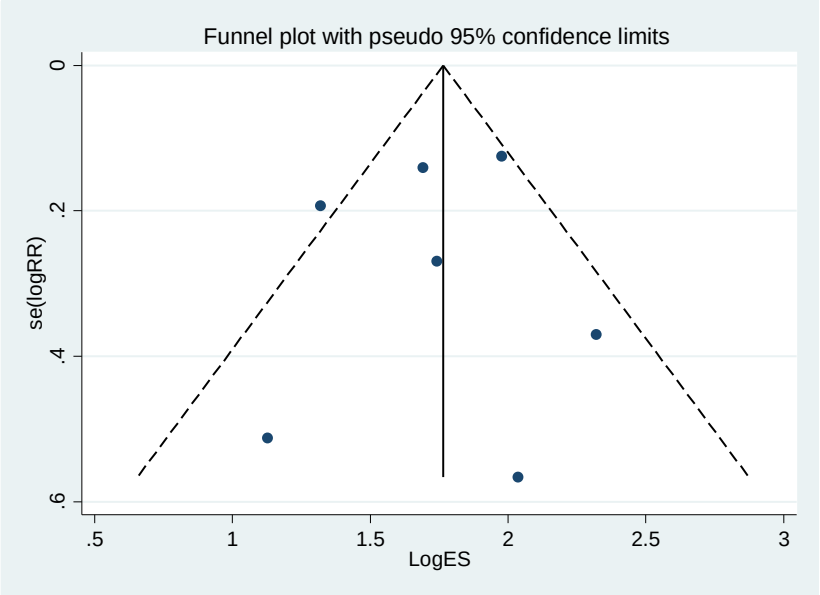


Figure 13: Funnel plot for participants who were obese and drinking above recommended limits of alcohol, compared to participants who were normal weight and drinking within limits

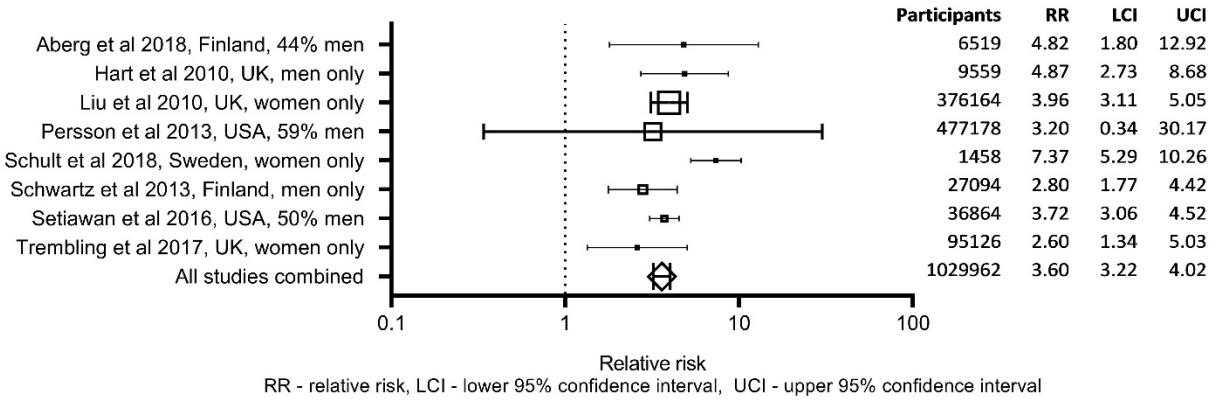


Figure 14: Relative risk of chronic liver disease in participants who are overweight and drinking above recommended limits of alcohol (>14 units/week), compared to those who are normal weight and drinking within recommended limits (>0 ≤14 units/week). I-squared = 61.3% (p = 0.012). Box size indicates weight study contributes.

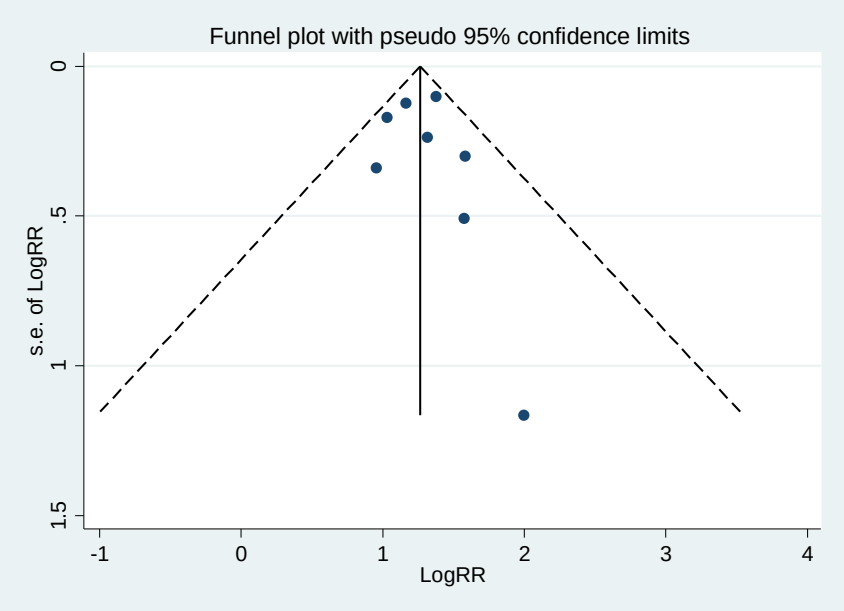


Figure 15: Funnel plot for participants who were overweight and drinking above recommended limits of alcohol, compared to participants who were normal weight and drinking within limits

Figure 16 shows the summary relative risks, for all studies combined, for overweight, obesity, above limits alcohol consumption and combinations of these risk factors. These have also been depicted in an infographic, the aim of which is to convey the message in a way that is simple for patients and the public to understand (Figure 17).

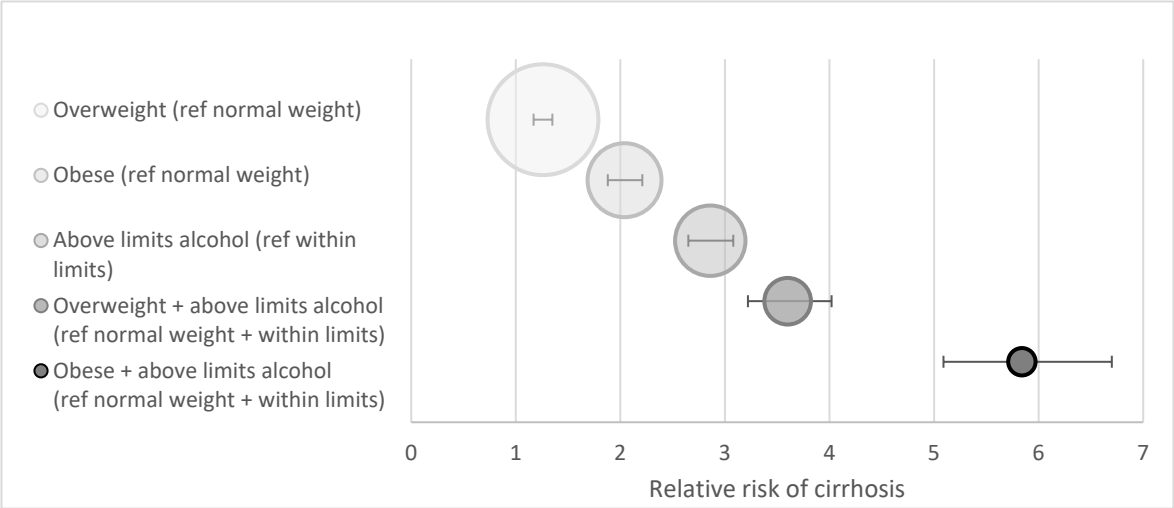


Figure 16: Pooled relative risk of chronic liver disease, all studies combined, for participants with differing alcohol and BMI risk factors. Reference groups are normal weight, within limits alcohol consumption, or both. Bubble size shows number of participants in each category. Error bars show 95% confidence intervals.

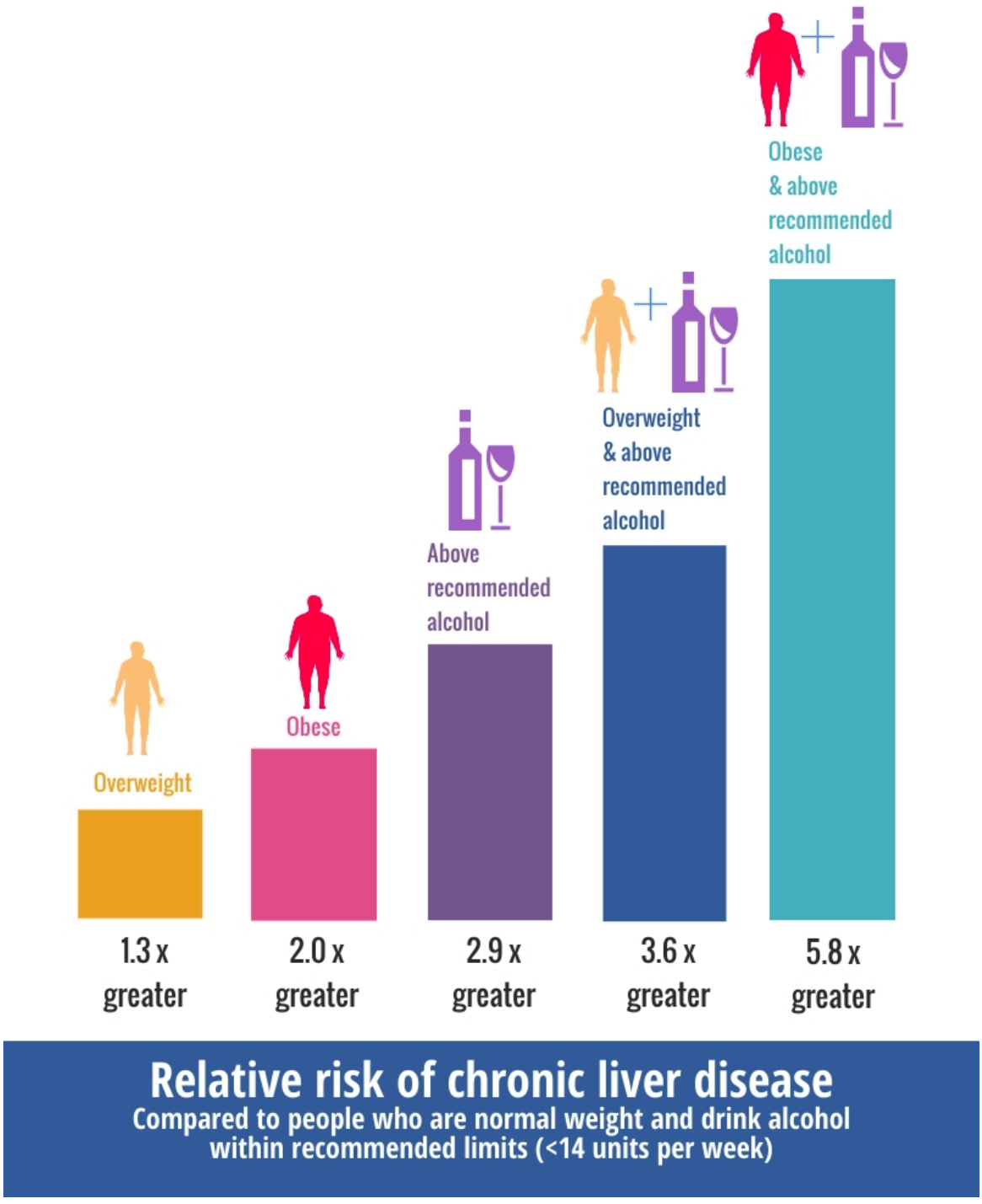


Figure 17: Infographic conveying key message for healthcare professionals, patients and the public

2.5 Discussion

This analysis showed no evidence of statistical interaction between alcohol consumption and BMI on risk of chronic liver disease. The effects were independent, but multiplicative. The meta-analysis demonstrated a significantly increased risk of chronic liver disease for people who have a combination of alcohol and BMI risk factors. Importantly, this increased risk was associated with only moderately raised BMI (>25) and alcohol consumption levels (>14 units per week). The analysis has shown that alcohol and BMI work multiplicatively such that the risk from both increased alcohol and increased BMI is the product of the two individual risks. This is supported by similar findings from three of the five eligible studies that considered combined effects.[59 74 79] In the other two studies, similar findings were found in moderate but not in higher risk alcohol consumers.[73 80] Absolute risk of chronic liver disease in the reference group (normal weight and drinking within limits alcohol consumption) was less than 1% in all included studies, over the follow-up period of the studies (range mean 5.5 to 33 years).

It was only possible to look at the difference between intermediate and higher risk alcohol consumers in one study (Table 15). This sub-group analysis showed that the risk of chronic liver disease is significantly higher for high risk, compared to intermediate risk alcohol consumers, within both overweight and obese categories of participants. Although caution should be exercised as this was only one study, the finding is plausible.

The terms interaction and synergy have been used interchangeably in the literature, which is confusing. Synergy is defined as “the production by two or more agents… of a combined effect greater than the sum of their separate effects”.[83] The combined effect for BMI and alcohol is the product of their separate effects. This may be greater than the sum of their separate effects (as found here in obese participants drinking above limits alcohol), or it may be less than the sum of their separate effects (as found here in overweight participants drinking above limits alcohol). Given the finding of multiplicative risk, it seems reasonable to say that alcohol and increased BMI act synergistically on risk of liver disease. As this study used observational data, it is not possible to detect biological interaction, only statistical interaction. We therefore state our results in terms of statistical interaction. No evidence of statistical interaction between BMI and alcohol was found. Some studies have described as ‘interaction’, a combination of BMI and alcohol which increases the risk of chronic liver disease over and above simple multiplicative effect.[59 60] These studies used methods[84 85] which have been discussed in the statistical methods section. Briefly, the method does not test for statistical interaction, but is reflecting multiplicative risk.

Liver disease is currently categorised separately as 'alcoholic liver disease ARLD' or 'non-alcoholic fatty liver disease NAFLD' and pathways in to secondary care often reflect these silos. The term BAFLD 'Both Alcohol and Fatty Liver Disease' is proposed here, to describe people who have a combination of increased BMI (>25) and moderate alcohol consumption. These people are often missed in clinical pathways, as they are drinking too much alcohol to meet the criteria for non-alcoholic fatty liver disease (<14 units/week), but they are not drinking enough alcohol to be considered at risk of alcoholic liver disease (>35 units/week women >50 units/week men). This large group of the population are at significantly increased risk of chronic liver disease and healthcare professionals must be aware of this, to ensure that they are appropriately assessed.

2.5.1 Strengths and Limitations

This study used data from prospective cohort studies, with a total of more than one million participants. One cohort was small, with only 11 cases of chronic liver disease. Such a small number of cases may not accurately reflect distribution across BMI and alcohol categories. The gender distribution within cohorts varied, and ethnicity was described in very few. The predominant ethnic group in the included cohorts is likely to be Caucasian and these results may not be generalisable to other ethnicities. However, one cohort was entirely made up of participants of Hispanic ethnicity and the effect size in this cohort was similar to others. Excluding this cohort from the analysis did not alter the effect estimates. Cohort studies yield observational data and therefore only associations between risk factors and liver disease outcomes can be described, causation cannot be proven.

Where necessary, data were requested directly from authors. Many of these studies had primary outcomes which were not looking at combined effects of alcohol and BMI. Risk of publication bias and selective reporting bias is therefore low, which was confirmed by visual inspection of the funnel plots and formal statistical tests. A one-stage meta-analysis technique was used. The one-stage approach combines all the data in a single meta-analysis based on a regression model stratified by study. This provides a more appropriate analysis and gives more accurate estimates of effect size, as the original count data from each study are combined in analysis, to determine the relative risk structure. It was not possible to adjust for any variables other than BMI and alcohol, as individual participant data on other variables were not available. This reduces the risk of statistical heterogeneity due to different studies adjusting for different variables, but there may be confounding effects. Age groups were similar across the included cohorts and results from single sex and mixed cohorts did not differ significantly. The primary outcome was cirrhosis. All

studies apart from one also included patients with HCC in their outcome data. However as incidence of HCC is low, this should not have unduly influenced results. Any effect due to this would have underestimated risk.

Finally, a significant limitation, as so often in this field, is the quality and consistency of alcohol data. Both alcohol and BMI data were collected at baseline, and may have changed over the follow-up period. Alcohol consumption data were self-reported in all studies, and may not be accurate. BMI data were self-reported in some studies. The questions asked of participants in relation to alcohol consumption were varied and some were non-specific. With the categorical data available we were only able to look at above limits alcohol consumption and could not differentiate between moderate and higher risk drinkers, except in a sub-group analysis of one study. This is an important area for further work in these high risk groups.

2.5.2 Discussion of statistical methods

The methods used in this analysis have been used in the belief that they are the best possible methods to use with the available data, and to answer the questions posed. However, there are other methods which have previously been used to describe similar effects. These are briefly discussed here. A more detailed explanation is included in Appendix A.

In an additive approach, such as risk difference, the model for risk would be solely due to the main effects. So the risk difference between $\mathrm{P11}$ (both risk factors present) and $\mathrm{P00}$ (reference, no risk factors present) is α+β, where α would represent BMI and β would represent alcohol consumption. This model allows for an interaction term (αβ) but not for multiplicative effects. It is also difficult to achieve feasible parameter estimates with this model, hence the log-linear model has several advantages.

Another approach which has been used, defines the relative excess risk due to interaction (RERI).[59 60 84-86] The relative risk is modelled as $\mathrm{P11} \,/\, \mathrm{P00} = \alpha + \beta$ in the case of no excess. In the presence of excess, the relative risk is modelled as $\mathrm{P11}/\mathrm{P00} = \alpha + \beta + (\alpha\beta)$. In principle this approach is possible, but it leads to a mix of scales as $\mathrm{P11} = \mathrm{P00}\ (\alpha{+}\beta)$ which shows that $\mathrm{P11}$ is dependent additively on factors A and B but also multiplicatively on the baseline risk $\mathrm{P00}$. The standard log linear model is therefore deemed superior, and has enough ability to show multiplicativity of effects even if there is no interaction. For completeness, part of this analysis was also performed using the RERI approach. Results were broadly similar but the log linear model enabled tighter estimates of risk.

2.5.3 Conclusion

The majority of liver disease is known to be preventable. Alcohol and obesity are two of the three main risk factors for liver disease, and they are also risk factors for many other chronic diseases. Identification of those at risk of liver disease, targeted testing and primary prevention measures to modify risk behaviours, are needed to improve patient outcomes. Currently available risk stratification tools do not reflect the multiplicative risk of liver disease, from a combination of alcohol consumption and increased BMI, which has been demonstrated in this analysis. Correctly identifying those who are at risk is the first step in early identification of disease, and the author suggests that this multiplicative risk should be reflected in risk assessment tools or practices.

Understanding of the aetiology of liver disease in the general population is known to be low.[46] Patients and health professionals need to be aware of the increased risk of liver disease associated with a combination of increased alcohol consumption and increased BMI. Understanding of this risk should be integrated in to lifestyle advice given to patients, risk assessment and stratification, clinical referral pathways and in national policy and guidelines. The infographic created here could be helpful in conveying risk to the general population. However, concepts such as relative risk (and the difference between absolute and relative risk) may not be easily understood. Work with Patient and Public Involvement groups, and colleagues who specialise in communicating risk, would be important in designing an infographic to clearly convey information about the risk of liver disease associated with increased alcohol consumption and increased BMI.

There may be implications for public health policy from these findings. Current guidelines for alcohol consumption, which are generic, may not be appropriate for overweight and obese patients. The same may be true for patients with diabetes or metabolic syndrome, who are at high risk of fatty liver disease. Policy makers should perhaps think about tailored guidance for specific risk groups, taking account of multi-morbidity.

Addressing the dual risk factors of alcohol and obesity has many population level benefits. As well as liver disease, they are causative agents in a number of other chronic diseases including heart disease, some cancers and dementia. Communicating risk to patients and policy makers can be difficult, particularly when the evidence is complex and equivocal. Our understanding of the relationship between alcohol consumption and health has changed over the last two decades, as more evidence has become available. The advice that has been given to patients, as a result of this evidence, has also changed which may have caused confusion. Clear messages need to be

communicated in order for primary prevention measures to be effective. We suggest that the evidence presented here provides the foundation for a clear message about the increased risk of liver disease due to a combination of alcohol consumption above recommended limits, and increased BMI.

2.6 Summary and next steps

This work has demonstrated the increased risk of liver disease in those people who are overweight or obese and drink alcohol above the recommended UK limits. For the public health significance of these results to be interpreted correctly, there was a need to identify what proportion of the population are in this increased risk group.

The next chapter describes data from an annual health survey in England, which is designed to be representative of the general population living in private households. From these survey data, the proportion of the population with single and multiple risk factors for liver disease has been described; the proportion of the population who have the joint risks of alcohol and increased BMI has been described; associations between risk factors and the results of non-invasive tests for liver disease, in participants with differing risk factor profiles, has also been described.

Chapter 3: Towards a better understanding of identification and prevention of liver disease in the general population: analysis of the Health Survey for England

3.1 Research objectives

1. To describe the proportion of the general population of England, who have one or more risk factors for liver disease. To describe how these risk factors co-cluster.

2. To explore the results of non-invasive tests for liver disease in the general population, by sociodemographic variables and by risk factor categories.

3.2 Background

The Lancet Commission on liver disease and others have called for earlier diagnosis of liver disease in primary care and community screening of high risk individuals, but despite innovative approaches in some areas, the best way to detect early liver disease in the general population is not clear. [9 61 87 88] Primary care professionals are often faced with difficult decisions about how to identify, manage or appropriately refer patients, with limited tools at their disposal, which they find challenging.[89]

As discussed in chapter 1, section 1.4, there are a range of diagnostic tests available for liver disease, which have advantages and disadvantages (Table 2). Routine blood tests can be combined with each other +/- patient demographic information such as age, to create proxy 'markers' of liver fibrosis. Most evidence on the diagnostic performance of fibrosis markers comes from populations of patients with defined liver pathology.[90 91] The performance and interpretation of these scores in the general population is unknown, yet liver blood tests and fibrosis markers are often used as part of risk algorithms or strategies to detect and manage early liver disease in primary care. Liver markers which have been better validated, such as ELF® and Fibroscan, are either not widely available in primary care, or their availability varies greatly between regions. Better understanding of the distribution of risk factors, liver blood tests and fibrosis scores in the general population is needed.

The Health Survey for England (HSE) is a cross-sectional, annual assessment of the health and lifestyle of approximately 8,000 adults, of whom around half also have a blood sample taken.[92 93] For the first time in 2016 alanine aminotransferase (ALT), aspartate aminotransferase (AST) and platelet tests were included in the assessment. This allows analysis of basic liver blood markers, as well as calculation of compound fibrosis scores which use a combination of blood test results plus or minus patient demographic information.

The HSE data provide a unique opportunity to improve knowledge and understanding of risk factors for, and non-invasive markers of, liver disease in people outside healthcare settings.

3.3 Methods

3.3.1 Sample and measurements

Full details of the Health Survey for England (HSE) 2016 survey methods are available elsewhere.[92] [94] Data are available without charge from the UK Data Service.[93] The HSE is an annual, multi-stage, stratified, random probability sample designed to be representative of the population living in private households in England. Data were collected at interviews, which included self-completion questionnaires. The interviews were followed by a nurse visit, which included further questions (including about liver disease), measurements (including waist circumference) and a request to provide a blood sample. For the first time, in the 2016 survey, blood samples were tested for AST, ALT and platelet count.

This analysis included the 7,826 adults aged 18 years and over who were in the sample. Of these, 3,791 (48%) had a blood test taken and valid results were available for ALT n=3,676; AST n=3,500 and Platelets n=3,676.

3.3.2 Sociodemographic and socioeconomic variables

Available data included age, sex, ethnicity, employment, education level and deprivation. Age (in ten year groups) and sex were used as provided in the HSE dataset. Ethnicity was re-grouped in to four categories as: White, Black, Asian and Mixed/multiple/other. Employment was categorised using the National Statistics Socioeconomic Classification (NSSEC), divided into three categories: Professional (managerial and professional occupations), intermediate (intermediate occupations), and routine (routine and manual occupations). Educational qualifications were grouped as: degree (NVQ4/NVQ5/Degree or equivalent), below degree, and no qualification. Area-level deprivation was categorised using Index of Multiple Deprivation 2015 (IMD) national quintiles: one (least deprived) to five (most deprived).

3.3.3 Risk factor variables

Data on risk factors came from interview, self-reported questionnaire and nurse visit with or without a blood test. Physical activity was self-reported at interview. Interviewers measured the height and weight of all adult participants, from which Body Mass Index (BMI) was derived using the following formula: BMI = weight in kg / [height in metres].^{2} BMI was grouped, excluding

underweight participants, as normal weight (BMI ≥18.5 to <25), overweight (25 to <30) and obese (≥30). Waist circumference was measured in centimetres and was stratified as low (<94 male, <80 female), high (94-102 male, 80-88 female), very high (>102 male, >88 female).[95] Alcohol consumption was self-reported (full details are in HSE documentation, Appendix B). Briefly, participants were asked what types of alcohol they had drunk, size of receptacle (can/bottle/glass) and how often they usually drank each type, per week, over the past 12 months. The HSE survey team calculated units of alcohol per week from these responses. Categories of alcohol consumption used in this analysis were: none (non-drinker or no alcohol in the last 12 months), lower risk (up to 14 units per week), increased risk (14-50 units per week male, 14-35 units per week female) and higher risk (>50 units per week male, >35 units per week female).[81] Alcohol consumption above recommended guidelines is >14 units per week in the UK, for both men and women.[68] Diabetes was defined as absent, present and diagnosed (participant told by a doctor that they had diabetes) or present but undiagnosed (hba1c ≥6.5% in the blood test but patient did not report having a diagnosis of diabetes). Self-reported smoking was categorised as current, ex-regular or never.

'Obesity risk' was defined as present if BMI≥25 and/or waist circumference was high or very high. 'Alcohol risk' was defined as present if alcohol consumption >14 units/week (UK recommended limit).[68] Participants were defined as at risk of Non-alcoholic fatty liver disease (NAFLD) if they met the criteria for obesity risk and they reported lower risk or no alcohol consumption. Participants were defined as at risk of Both Alcohol and Fatty Liver Disease (BAFLD) if they met the criteria for obesity risk and they reported increased risk alcohol consumption. Participants were defined as at risk of Alcohol Related Liver Disease (ARLD) if they reported higher risk alcohol consumption.

3.3.4 Liver blood tests and fibrosis markers

Blood samples were sent directly to a single laboratory by the participating nurse and were analysed. Platelet measurement, AST and ALT analyses were carried out in the Blood Sciences Department at the Royal Victoria Infirmary (RVI) in Newcastle. AST and ALT analyses were carried out using the Roche-Cobas assay. The optimised International Federation of Clinical Chemistry (IFCC) method was used, without pyridoxal phosphate activation.[94] ALT and AST were defined as high if >40 IU/L for both men and women, as per the North East Pathology Network Harmonized range which is used by the RVI laboratory. Although lower cut offs may be used elsewhere, accuracy can only be assured when using the ranges specified by an individual laboratory for their

methods. National guidelines do not give a value for abnormality, but state that laboratory reference ranges should be used to determine an abnormal result.[58]

Liver fibrosis scores were calculated as follows:

AST:ALT ratio as AST(IU/L)/ALT(IU/L).

AST to Platelet Ratio Index (APRI) as [(AST(IU/L)/AST upper limit of normal) / platelets(x10^9/L)] x 100[23]

Fibrosis-4 (FIB-4) score as (age in yrs x AST) / (platelet count x √ALT).[22] Age data are provided in five yearly categories. We used the mid-point of each age category to assign a specific age to participants in order to calculate FIB-4. For example, those in the age category 70-74yrs were assigned 72.5 yrs.

BARD score was the sum of: AST/ALT ratio≥0.8 = two points, BMI≥28 = one point, diabetes = one point.

The following thresholds were used for liver fibrosis scores. FIB-4 was defined as high if FIB-4>2.67 and low if FIB-4<1.30[96-98]; APRI was defined as high if APRI≥1.0[24]; AST:ALT ratio was defined as high if ≥1.0[24 99 100]; AST:ALT ratio if LFT abnormal was defined as high if AST:ALT ratio≥1.0 AND either ALT or AST was >40 IU/L. BARD score was defined as high if ≥2.[24 97 100]

FIB-4, AST, ALT, APRI and AST:ALT ratio were grouped as binary variables (high/not high) for logistic regression analysis.

3.3.5 Statistical analysis

Appropriate survey data techniques to account for sampling weights, clustering and stratification of the sampled data (using the survey data analysis tools in STATA version 14.2) were used in all analyses. Survey weightings, provided in the HSE dataset, were used to take account of survey design and non-response, including those who did or did not have a blood test.[94] Using these weights and survey data techniques in the analysis ensures that the results are representative of the whole population of England and are truly generalisable to people living in private households.

Descriptive statistics were used to describe the socio-demographic, lifestyle and clinical characteristics of the study population and those with risk factors for liver disease (obesity risk, diabetes, alcohol risk). Chi squared tests were used to check for independence within groups.

Weighted proportions were used to describe the age and sex distribution of liver blood tests and fibrosis markers; the proportion with a 'high' liver blood test or fibrosis marker result amongst different risk groups; and the overlap of risk factors in the study population. Median values for liver blood tests and fibrosis markers (with 95% confidence intervals, as using survey estimate techniques), were used to describe their distribution within BMI and alcohol consumption categories.

Weighted proportions were used to compare the proportion of the population within different risk groups, who had been told they were at risk of liver disease.

Age-sex adjusted logistic regression models were used to examine the associations between liver blood tests /fibrosis markers and socio-demographic, clinical and lifestyle factors in the population. Odds ratios are presented with 95% confidence intervals and statistical significance at two levels (0.05 and 0.01) is indicated.

3.4 Results

3.4.1 Liver disease risk factors

Baseline characteristics of the population representative sample are presented in Table 16. Some 23.5% of participants (31.4% of males and 16.0% of females) consumed more alcohol than the recommended guidelines (>14 units per week).[68] 63.8% of participants (68.2% of males and 59.2% of females) were overweight or obese (BMI≥25) and 66.1% had a high or very high waist circumference.

Multiple risk factors for liver disease were common (Table 16) with nearly 90% of the sample having at least one risk factor for liver disease (alcohol risk, obesity risk, diabetes) and 28% having two or more risk factors. The proportion with multiple risk factors varied significantly by age, sex, ethnicity, employment, education and smoking. The proportion of men with two or more risk factors was almost twice as high as that for women. Within employment categories, the lowest proportion with multiple risk factors was in routine and manual workers. Within educational categories, the highest proportion with multiple risk factors was in those with lowest educational attainment.

Table 16: Baseline characteristics of the HSE sample of adults

		Whole sample		At least one risk factor[§]			Two or more risk factors[§]		
Variable categories		weighted n for whom data available	% of whole sample in variable category – weighted proportion	weighted n for whom data available	% in variable category who have at least one risk factor - weighted proportion	Chi squared p value	weighted n for whom data available	% in category who have two or more risk factors - weighted proportion	Chi squared p value
Whole sample		7743		5738	89.2%		4635	28.4%	
Age	18-24yrs 25-34yrs 35-44yrs 45-54yrs 55-64yrs 65-74yrs 75+ yrs	7743	10.7% 17.4% 16.6% 18.2% 14.8% 12.6% 9.7%	5738	79.3% 83.7% 86.6% 91.4% 92.4% 93.6% 95.6%	<0.001**	4635	11.4% 18.3% 23.8% 32.0% 39.2% 36.5% 36.7%	<0.001**
Sex	Male Female	7743	48.9% 51.1%	5738	90.9% 87.4%	<0.001**	4635	37.1% 19.7%	<0.001**
Ethnicity	White Black Asian Mixed/multiple/other	7721	86.5% 3.4% 7.4% 2.7%	5732	89.6% 92.5% 83.1% 90.9%	0.013*	4630	30.4% 18.2% 10.9% 19.8%	<0.001**
Employment (NSSEC)	Professional Intermediate Routine	7286	36.2% 25.2% 38.6%	5485	88.6% 88.6% 90.8%	0.053	4427	30.6% 30.6% 26.8%	0.049*
Index of multiple deprivation	Least deprived 2nd 3rd 4th Most deprived	7743	19.2% 18.9% 21.9% 19.3% 20.7%	5738	87.7% 87.9% 88.5% 90.4% 91.9%	0.056	4635	29.0% 30.2% 28.0% 28.4% 26.4%	0.703
Education	NVQ4/NVQ5/degree or equivalent Below degree No qualification	7718	29.6% 50.3% 20.1%	5731	85.4% 89.6% 94.3%	<0.001**	4634	24.6% 29.9% 31.2%	<0.001**

Variable categories		Whole sample		At least one risk factor[§]			Two or more risk factors[§]		
		weighted n for whom data available	% of whole sample in variable category – weighted proportion	weighted n for whom data available	% in variable category who have at least one risk factor - weighted proportion	Chi squared p value	weighted n for whom data available	% in category who have two or more risk factors - weighted proportion	Chi squared p value
Smoking	Current Ex-regular Never	7711	18.0% 25.7% 56.3%	5734	90.6% 93.5% 86.7%	<0.001**	4635	29.9% 40.1% 22.4%	<0.001**
Physical activity MVPA	Inactive Low or some activity Meets MVPA guidelines	7681	22.9% 15.4% 61.7%	5692	93.6% 90.1% 87.6%	<0.001**	4600	31.3% 28.7% 27.6%	0.146
Alcohol consumption	Non-drinker / not in last 12 months Lower risk (up to 14 units/week) Increased risk (14-50 male, 14-35 female) Higher risk (more than 50 male, 35 female)	7604	18.6% 57.9% 19.2% 4.3%						
Body Mass Index (BMI)	BMI category: Normal 18.5 to <25 Overweight 25 to <30 Obese ≥30	6236	36.3% 36.6% 27.2%						
Waist circumference (NICE categorisation)[95]	Low (<94cm men, <80cm women) High (94-102 men, 80-88 women) Very high (>102 men, >88 women)	4122	33.9% 24.4% 41.7%						
Diabetes	No diabetes Doctor diagnosed undiagnosed	3607	90.3% 6.6% 3.1%						

[§] Risk factors are BMI≥25, high or very high waist circumference, diagnosed or undiagnosed diabetes, alcohol consumption >14 units/week

The proportion of participants in different risk factor categories, by sociodemographic variables, is shown in Table 17 and Table 18. The proportion of participants with no risk factors varied significantly by age, sex, employment, index of multiple deprivation, education, smoking and physical activity. The proportion of the sample with no risk factors decreased with increasing age, was highest in professionals, decreased with decreasing educational attainment, was highest in participants who had never smoked and increased with increasing physical activity.

The proportion of participants with risk factors for NAFLD (low risk or no alcohol consumption + high/very high waist circumference or BMI≥25) varied significantly by age, sex, ethnicity, employment, index of multiple deprivation, education, smoking and physical activity. The proportion of participants at risk of NAFLD increased with increasing age, was higher in females, was highest in participants of black ethnicity, was highest in participants in routine/manual employment, increased with increasing deprivation, increased with decreasing educational attainment, was highest in participants who had never smoked and decreased with increasing physical activity.

The proportion of participants with risk factors for BAFLD (intermediate alcohol consumption + high/very high waist circumference or BMI≥25) varied significantly by age, sex, ethnicity, employment, index of multiple deprivation, education, smoking and physical activity. The proportion of participants at risk of BAFLD was highest in those aged 55-64yrs, was more than twice as high in males, was highest in participants of white ethnicity, was highest in participants in professionals, was lowest in the most deprived, decreased with decreasing educational attainment, was lowest in those who had never smoked and increased with increasing physical activity.

Table 17: Baseline characteristics of sample by risk category – no risk, at risk of NAFLD, at risk of BAFLD

		No risk factors n=1646			At risk of NAFLD n=3364			At risk of BAFLD n=909		
Variable categories		weighted n for whom data available	% in variable category who have no risk factors – weighted proportion	Chi squared p value	weighted n for whom data available	% in variable category who are at risk of NAFLD- weighted proportion	Chi squared p value	weighted n for whom data available	% in variable category who are at risk of BAFLD - weighted proportion	Chi squared p value
Whole sample		4373	37.4%		6431	49.9%		7230	12.2%	
Age	18-24yrs 25-34yrs 35-44yrs 45-54yrs 55-64yrs 65-74yrs 75+ yrs	3342	80.4% 65.8% 56.9% 46.0% 39.5% 37.7%	P<0.001**	6431	30.4% 41.0% 49.9% 54.8% 52.2% 58.2% 63.7%	P<0.001**	7230	5.9% 9.8% 11.7% 12.6% 17.8% 15.6% 10.3%	P<0.001**
Sex	Male Female	3342	55.3% 47.6%	P<0.001**	6431	44.9% 55.0%	P<0.001**	7230	17.3% 7.4%	P<0.001**
Ethnicity	White Black Asian Mixed/multiple/other	3336	50.8% 43.3% 58.9% 54.6%	P=0.174	6426	48.7% 63.0% 59.3% 48.3%	P<0.001**	7222	13.5% 5.2% 2.4% 8.6%	P<0.001**
Employment	Managerial Intermediate Routine	3165	56.8% 50.9% 45.2%	P<0.001**	6113	44.9% 50.3% 55.1%	P<0.001**	6820	15.7% 13.7% 9.3%	P<0.001**
Index of multiple deprivation	Least deprived 2nd 3rd 4th Most deprived	3342	55.1% 53.7% 54.1% 48.2% 45.4%	P=0.025*	6431	47.8% 48.5% 47.3% 50.1% 55.9%	P=0.002**	7230	13.8% 14.2% 13.0% 11.9% 8.4%	P<0.001**

		No risk factors n=1646			At risk of NAFLD n=3364			At risk of BAFLD n=909		
Variable categories		weighted n for whom data available	% in variable category who have no risk factors – weighted proportion	Chi squared p value	weighted n for whom data available	% in variable category who are at risk of NAFLD- weighted proportion	Chi squared p value	weighted n for whom data available	% in variable category who are at risk of BAFLD - weighted proportion	Chi squared p value
Education	NVQ4/NVQ5/degree or equivalent Below degree No qualification	3340	63.5% 50.0% 34.0%	P<0.001**	6424	42.7% 49.4% 63.2%	P<0.001**	7220	13.4% 13.2% 8.2%	P<0.001**
Smoking	Current Ex-regular Never	3342	47.6% 43.0% 65.5%	P<0.001**	6431	43.0% 49.5% 52.2%	P<0.001**	7230	11.6% 18.5% 9.5%	P<0.001**
Physical activity MVPA	Inactive Low or some activity Meets MVPA guidelines	3310	33.6% 46.0% 57.9%	P<0.001**	6387	63.0% 54.8% 44.6%	P<0.001**	7174	7.2% 11.7% 14.3%	P<0.001**

NVQ – National Vocational Qualification MVPA – Moderate-intensity and Vigorous-intensity Physical Activity
* denotes significance at the 0.05 level and ** denotes significance at the 0.01 level
No risk factors = low risk or no alcohol consumption + low waist circumference + BMI<25 + no diabetes diagnosed or undiagnosed
At risk of NAFLD = low risk or no alcohol consumption + high/very high waist circumference or BMI≥25
At risk of BAFLD = intermediate alcohol consumption + high/very high waist circumference or BMI≥25

The proportion of participants with high alcohol risk (alcohol consumption >50 units/week for males and >35 units/week for females) varied significantly by age, sex, ethnicity and smoking (Table 18). The proportion of the sample with high alcohol risk was highest in participants aged 45-64yrs, was higher in males, was lowest in those with Asian or black ethnicity and was highest in current smokers.

The proportion of participants with high alcohol risk and obesity risk (high alcohol risk as above, plus high/very high waist circumference or BMI≥25) varied significantly by age, sex, ethnicity and smoking (Table 18). The proportion of the sample with high alcohol and obesity risk was highest in those aged 55-64yrs, twice as high in males, highest in participants of white ethnicity and lowest in participants who had never smoked.

The proportion of participants with diabetes risk (self-reported doctor diagnosed diabetes, or hba1c ≥ 6.5%) varied significantly by age, sex, employment, education, smoking and physical activity (Table 18). The proportion of participants with diabetes risk increased with increasing age, was higher in males, was highest in routine/manual workers, increased with decreasing educational attainment, was lowest in participants who had never smoked and decreased with increasing physical activity.

Table 18: Baseline characteristics of sample by risk category – high alcohol risk, high alcohol and obesity risk

		High alcohol risk n=338			High alcohol risk & obesity risk n=195			Diabetes risk n=389		
Variable categories		weighted n for whom data available	% in variable category who are at high alcohol risk - weighted proportion	Chi squared p value	weighted n for whom data available	% in variable category who are at high alcohol & obesity risk - weighted proportion	Chi squared p value	weighted n for whom data available	% in variable category who have diagnosed or undiagnosed diabetes	Chi squared p value
Whole sample		7604	4.3%		7505	1.5%		3509	10.1%	
Age	18-24yrs 25-34yrs 35-44yrs 45-54yrs 55-64yrs 65-74yrs 75+ yrs	7604	3.8% 2.4% 4.3% 5.8% 5.9% 4.3% 2.8%	P<0.001**	7521	1.20% 1.46% 2.06% 3.16% 3.96% 3.03% 1.66%	P<0.005**	3607	0.0% 1.9% 4.0% 10.9% 14.6% 16.6% 25.5%	P<0.001**
Sex	Male Female	7604	5.2% 3.4%	P=0.001**	7521	3.29% 1.61%	P<0.001**	3607	11.3% 8.1%	P=0.002*
Ethnicity	White Black Asian Mixed/multiple/other	7595	4.8% 0.73% 0.17% 4.4%	P<0.001**	7513	2.74% 0.31% 0.17% 1.77%	P<0.001**	3601	9.5% 15.0% 11.0% 7.8%	P=0.501
Employment	Managerial Intermediate Routine	7177	4.7% 4.0% 4.3%	P=0.529	7095	2.6% 2.6% 2.4%	P=0.860	3416	7.2% 9.8% 12.3%	P<0.001**
Index of multiple deprivation	Least deprived 2nd 3rd 4th Most deprived	7604	4.4% 3.7% 4.5% 4.1% 4.6%	P=0.822	7521	2.5% 2.4% 2.2% 2.7% 2.3%	P=0.940	3607	7.8% 10.1% 8.5% 9.7% 12.4%	P=0.074

Variable categories		High alcohol risk n=338			High alcohol risk & obesity risk n=195			Diabetes risk n=389		
		weighted n for whom data available	% in variable category who are at high alcohol risk - weighted proportion	Chi squared p value	weighted n for whom data available	% in variable category who are at high alcohol & obesity risk - weighted proportion	Chi squared p value	weighted n for whom data available	% in variable category who have diagnosed or undiagnosed diabetes	Chi squared p value
Education	NVQ4/NVQ5/degree or equivalent Below degree No qualification	7592	3.7% 4.8% 4.0%	P=0.145	7510	1.9% 2.8% 2.4%	P=0.124	3605	5.2% 9.0% 19.0%	P<0.001**
Smoking	Current Ex-regular Never	7604	7.6% 5.8% 2.5%	P<0.001**	7520	3.3% 3.5% 1.6%	P<0.001**	3607	10.8% 13.1% 7.8%	P<0.001**
Physical activity MVPA	Inactive Low or some activity Meets MVPA guidelines	7546	4.0% 3.8% 4.5%	P=0.536	7465	2.3% 1.9% 2.6%	P=0.387	3574	21.4% 10.1% 5.9%	P<0.001**

NVQ – National Vocational Qualification MVPA – Moderate-intensity and Vigorous-intensity Physical Activity

* denotes significance at the 0.05 level and ** denotes significance at the 0.01 level

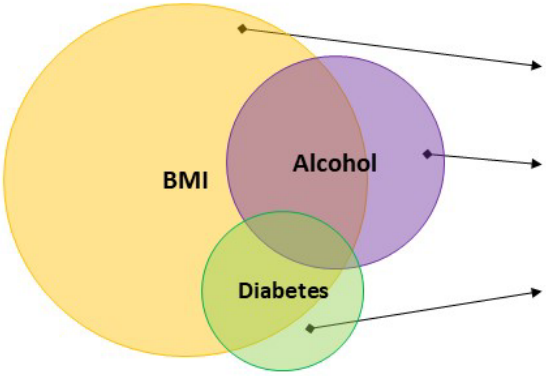
High alcohol risk = alcohol consumption >14 units/week

High alcohol risk & obesity risk = alcohol consumption > 14 units/week + high/very high waist circumference or BMI ≥25

Diabetes risk = self-reported doctor diagnosed diabetes or hba1c ≥ 6.5%

Overlap of risk factors is shown in Figure 17. Of participants in the highest risk category for alcohol consumption (4.3% of the sample): 6.6% also had diabetes, 29.8% were obese and 47.0% had a very high waist circumference.

Criteria for risk of NAFLD (obesity risk, lower risk alcohol consumption) were present in 50% of the population and a further 12.2% met the criteria for risk of BAFLD (obesity risk and increased, but not higher risk, alcohol consumption).



Risk factors	% in sample (weighted)
BMI ≥ 25	**63.7%**
BMI≥25 + alcohol≥14 units/wk	16.1%
BMI≥25 + diabetes	8.3%
Alcohol ≥ 14 units/wk	**23.5%**
Alcohol ≥ 14 units/wk + BMI ≥ 25	16.1%
Alcohol ≥ 14 units/wk + diabetes	1.9%
Diabetes	**10.1%**
Diabetes + BMI ≥ 25	8.3%
Diabetes + Alcohol ≥ 14 units/wk	1.9%

Figure 18: Overlap of risk factors for liver disease in the HSE study population (categories are not exclusive)

3.4.2 Liver blood tests and fibrosis risk scores

The proportion of abnormal liver blood tests and high fibrosis risk scores in the population varied from less than one percent to more than ninety percent, depending on the test/score (Figure 18). Above threshold results showed variability between different tests: FIB-4 (3.1% males, 1.9% females), ALT (13.6% males, 4.8% females), AST (7.2% males, 3.3% females) and APRI (0.9% males, 0.4% females). The AST:ALT ratio was high in 71% of participants (59.6% males, 81.7% females). The proportion with a high AST:ALT ratio, if either their AST or ALT were abnormal (>40 IU/L) was lower (3.13% males, 1.36% females). The BARD score was high in 88% of participants (81.1% males, 93.7% females).

Of the whole sample, 10.9% (95%CI 9.7 to 12.3%) had abnormal liver blood tests, with a raised ALT or AST. For ALT, AST, FIB-4 and APRI, a high result was more common in males (Figure 18).

The AST:ALT ratio was high in 71% of our sample. The BARD score, driven by the high proportion with a raised AST:ALT ratio, was high in 88%. Further analyses of these were not performed. Analyses focused on ALT, FIB-4 and APRI, with the inclusion of AST in regression analyses. ALT is the most commonly available liver blood test and AST may be requested alongside it. FIB-4>2.67 and APRI >0.5 have been shown to be associated with significantly increased risk of liver disease mortality over 23 years of follow up in the NHANES general population cohort.[98]

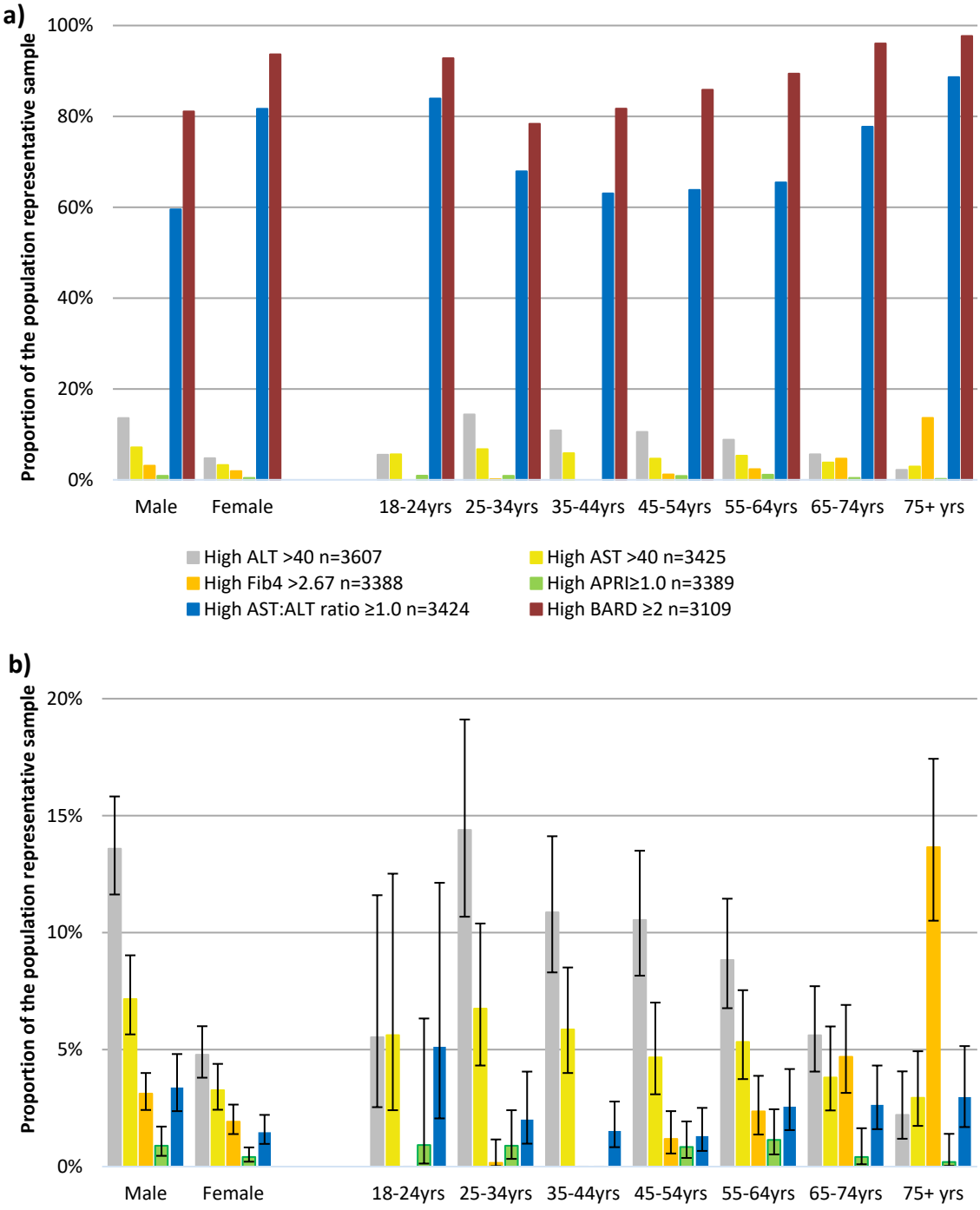


Figure 19: Distribution of 'high' liver blood test or fibrosis score results:

a) Including AST:ALT ratio and BARD

b) Excluding BARD and including AST:ALT ratio only for those with AST or ALT>40IU/L, with error bars showing 95% confidence intervals

ALT – alanine aminotransferase, AST – aspartate aminotransferase, Fib4 – Fibrosis 4 score, APRI – AST to Platelet Ratio Index, BARD – BARD score

Concordance between liver blood tests and non-invasive fibrosis tests was low. Of the 85 individuals who had a high FIB-4, only 11 also had a high ALT. Only seven individuals had high ALT, high FIB-4 and high APRI (Table 19).

Table 19: Overlap of participants with high score in different liver blood tests and fibrosis scores. Numbers shown are weighted n

	ALT>40	**FIB-4>2.67**	**APRI≥1.0**	**FIB-4>2.67 or APRI≥1.0**	**FIB-4>2.67 and APRI≥1.0**
	327	85	22	94	12
FIB-4>2.67	11		12		
APRI≥1.0	14	12			
FIB-4>2.67 or APRI≥1.0	18				
FIB-4>2.67 and APRI≥1.0	7				

The proportion of participants in the whole sample who had a raised ALT, FIB-4 or APRI, by risk factory category, are shown in Figure 20.

The proportion of participants with a raised ALT (n=327) was highest in those with high alcohol risk and obesity risk combined. The proportion of participants with a high ALT was significantly higher in all risk categories except NAFLD, than in the whole sample. The proportion was significantly lower in those with no risk factors, compared to the whole sample.

The proportion of participants with a high FIB-4 (n=85) was highest in those with diabetes risk, followed by those with high alcohol risk and obesity risk combined. The proportion was significantly higher than the whole sample only in those with diabetes risk. Compared to those with no risk factors, the proportion was significantly higher in those with high alcohol risk and obesity risk combined, and in those with diabetes risk.

The proportion of participants with a high APRI (n=22) was highest in participants with high alcohol risk and obesity risk combined. The proportion of participants with a high APRI was lower in the whole sample, than in those with no risk factors (but this difference did not reach statistical significance). Compared to the whole sample, the proportion with high APRI was significantly higher only in those with high alcohol and obesity risk combined.

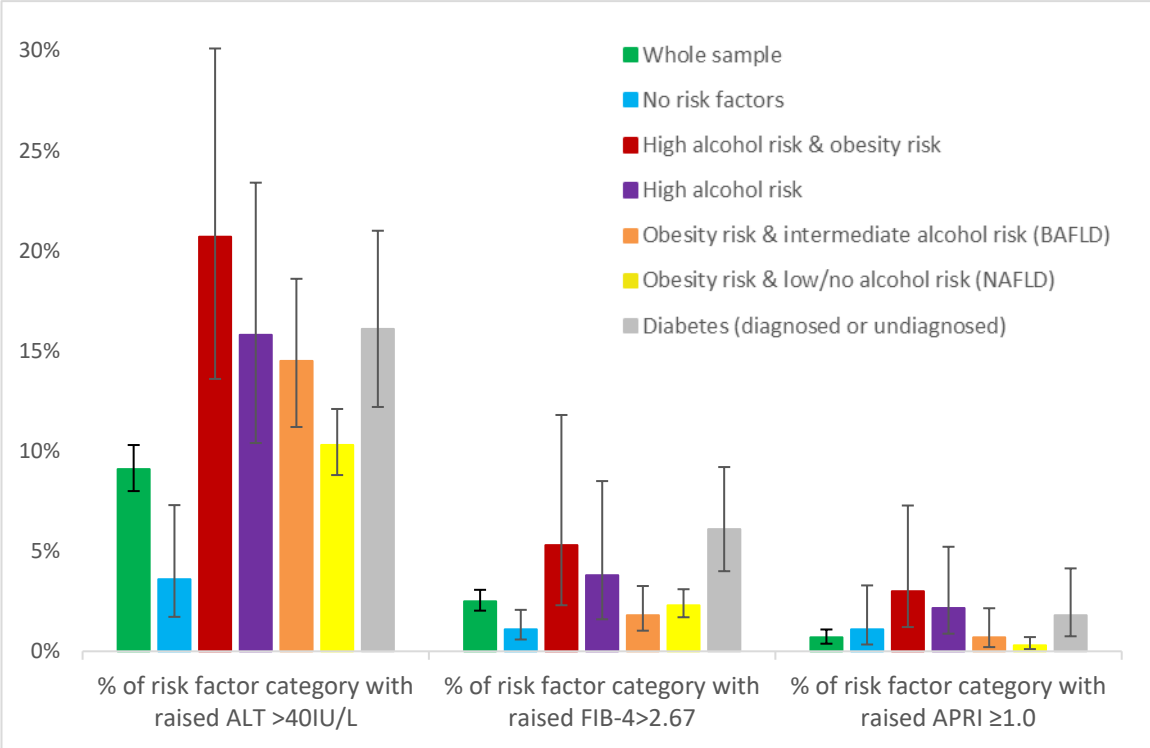


Figure 20: Proportion of the sample within risk factor categories, who have high ALT, FIB-4 or APRI. BAFLD and NAFLD categories are exclusive, other risk factor categories may overlap. Error bars show 95% confidence intervals.

The proportion of participants within each risk factory category, who had a high ALT, FIB-4 or APRI is stratified by gender in Table 20. The proportion of participants who had a high ALT result was significantly higher for males than females within all categories. The proportion of participants with a high result was highest in high alcohol and obesity risk combined, followed in order by diabetes, high alcohol risk, BAFLD and NAFLD. The proportion of males with a high ALT was larger than that for females, across all risk categories.

The proportion of participants who had a high FIB-4 result was significantly higher for males than females within the no risk factor category. The proportion of participants with a high result was highest in the diabetes risk group, followed in order by high alcohol and obesity risk combined, high alcohol risk, NAFLD and BAFLD.

The proportion of participants who had a high APRI result was not significantly different between males and females within any risk factor category. The proportion of participants with a high result was highest in the high alcohol and obesity risk combined group, followed in order by high alcohol risk, diabetes risk, BAFLD and NAFLD. The proportion of participants with a high result was lower in the NAFLD risk category, than in the whole sample.

Table 20: Proportion of participants, by risk factor category and gender, with high ALT, FIB-4 or APRI.

	% of risk factor category with raised ALT >40IU/L				% of risk factor category with raised FIB-4 >2.67				% of risk factor category with raised APRI ≥1.0			
Risk factor category	**Weighted n**	**All (95%CIs)**	**Male**	**Female**	**Weighted n**	**All**	**Male**	**Female**	**Weighted n**	**All**	**Male**	**Female**
Whole sample	3607	9.1% (8.0, 10.3)	13.6%	4.8%**	3388	2.5% (2.0, 3.1)	3.1%	1.9%	3389	0.7% (0.4, 1.1)	0.9%	0.4%
No risk factors	1697	5.2% (4.0, 6.8)	7.9%	2.1%**	1598	1.4% (1.0, 1.9)	2.0%	0.6%**	1598	0.6% (0.3, 1.5)	0.9%	0.3%
High alcohol risk & obesity risk	100	22.5% (14.8, 32.8)	28.4%	13.2%	95	5.9% (2.5, 13.2)	5.0%	7.4%	95	3.4% (1.4, 8.2)	2.5%	4.8%
High alcohol risk	155	15.8% (10.4, 23.4)	21.6%	8.5%*	148	3.8% (1.6, 8.5)	3.5%	4.2%	148	2.2% (0.9, 5.2)	1.8%	2.7%
Obesity risk & intermediate alcohol risk (BAFLD)	489	14.5% (11.2, 18.6)	18.2%	7.0%**	457	1.8% (1.0, 3.3)	1.4%	2.6%	457	0.7% (0.2, 2.2)	0.7%	0.5%
Obesity risk & low/no alcohol risk (NAFLD)	1719	10.3% (8.8, 12.1)	16.5%	5.5%**	1621	2.3% (1.7, 3.1)	2.9%	1.9%	1621	0.3% (0.1, 0.7)	0.2%	0.4%
Diabetes (diagnosed or undiagnosed)	343	16.2% (12.2, 21.0)	18.6%	12.9%	323	6.1% (4.0, 9.2)	7.1%	4.7%	323	1.8% (0.8, 4.1)	2.3%	1.1%

ALT – Alanine Aminotransferase FIB-4 – Fibrosis 4 score APRI – AST to Platelet Ratio Index

* indicates significance at the 0.05 level ** indicates significance at the 0.01 level

For those who consumed alcohol, within each BMI category, median values of ALT, FIB-4 and APRI increased with increasing alcohol consumption (Figure 21, Figure 22, Figure 23). Median FIB-4, ALT, and APRI in higher risk drinkers, were greater in participants who were also overweight or obese. The highest median values were found in obese participants with higher risk alcohol consumption.

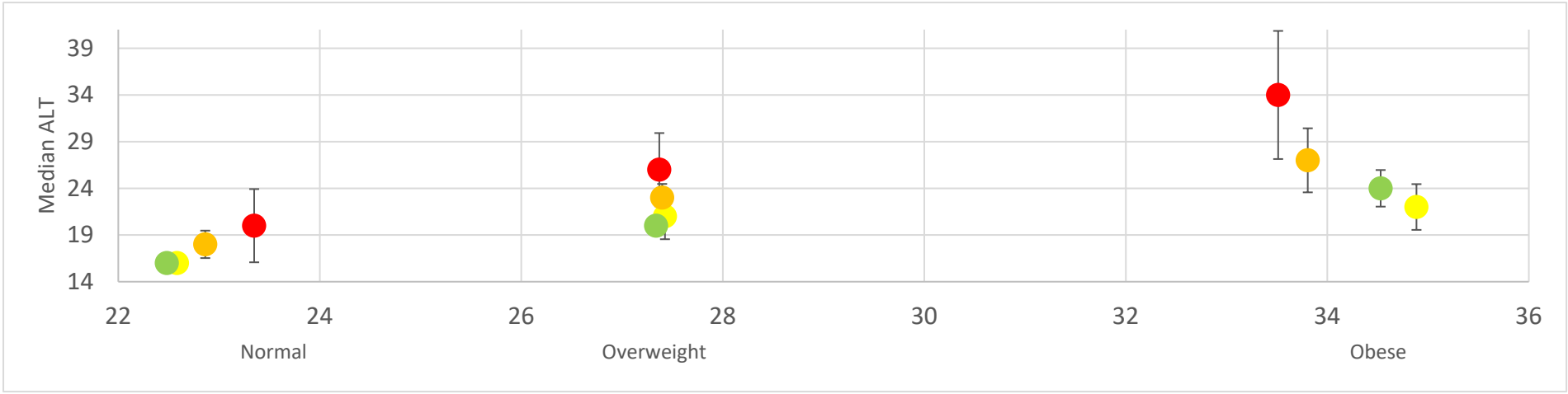


Figure 21: Median ALT, by BMI and alcohol consumption categories. Error bars show 95% confidence intervals around the median. BMI categories are Normal 18.5 to <25, Overweight 25 to <30, Obese ≥30, with BMI plotted as the mean within each category.

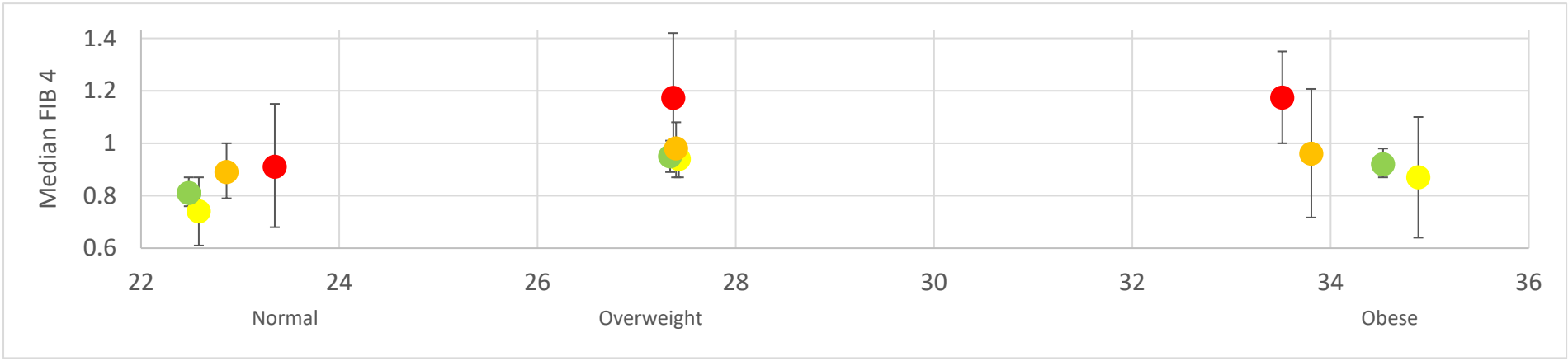


Figure 22: Median FIB-4, by BMI and alcohol consumption categories. Error bars show 95% confidence intervals around the median. BMI categories are Normal 18.5 to <25, Overweight 25 to <30, Obese ≥30, with BMI plotted as the mean within each category.

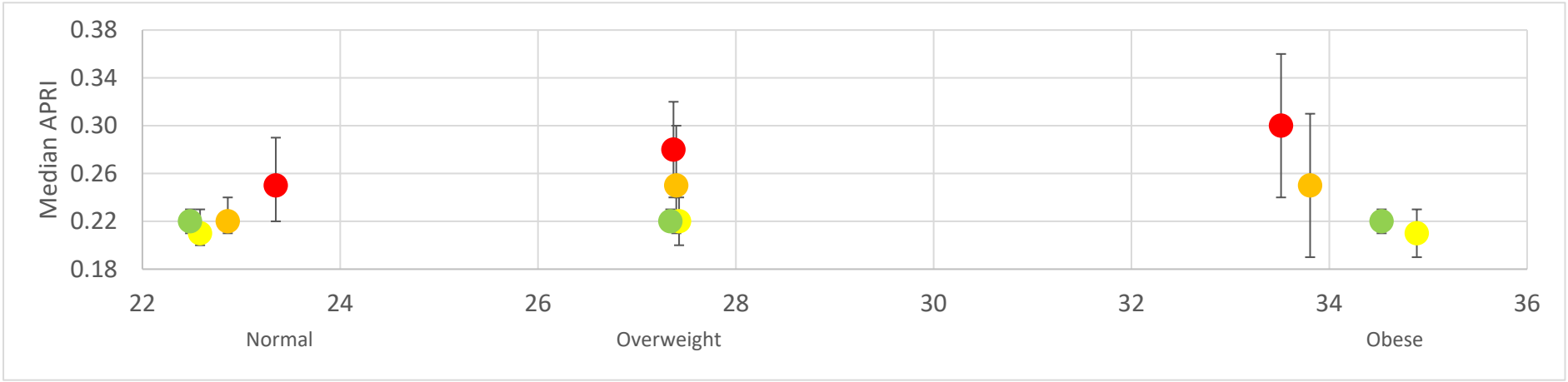


Figure 23: Median APRI, by BMI and alcohol consumption categories. Error bars show 95% confidence intervals around the median. BMI categories are Normal 18.5 to <25, Overweight 25 to <30, Obese ≥30, with BMI plotted as the mean within each category.

3.4.3 Awareness of liver disease

Of the whole sample, 4.4% of participants reported ever being told they were at risk of liver disease. Among risk factor groups, the highest proportion who had been told they were at risk of liver disease was diagnosed diabetics (15.9%). The lowest proportion was in those with NAFLD (4.7%) or BAFLD (4.9%) risk factors, compared to other risk categories. The highest proportion who reported having been tested for liver disease was diagnosed diabetics (30.0%), followed by those with a combination of high risk alcohol consumption and obesity (23.8%). The lowest proportion reporting having been tested for liver disease was in those with NAFLD (14.2%) or BAFLD (16.3%) risk factors, compared to other risk categories.

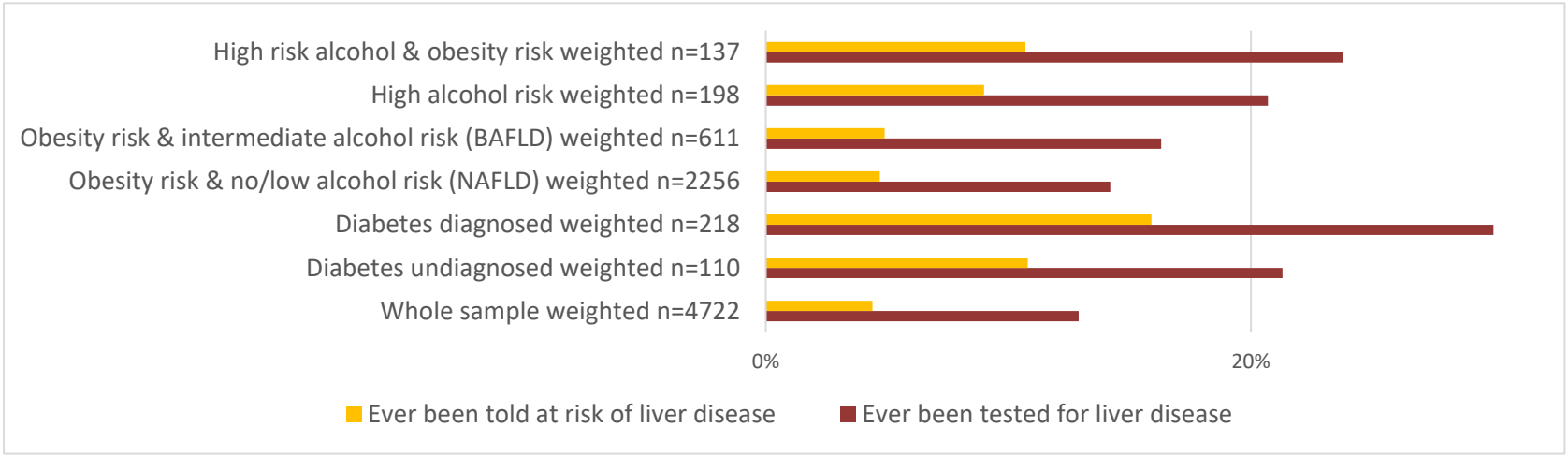


Figure 24: Proportion of the sample, within risk factor categories, who reported ever being told they were at risk of liver disease and reported ever being tested for liver disease.

3.4.4 Regression modelling

3.4.4.1 Logistic regression models

In the univariate logistic regression model, high ALT was significantly associated with younger age, male sex, Asian ethnicity, increasing BMI, increasing waist circumference, decreasing central obesity, undiagnosed diabetes, and increasing alcohol consumption. When adjusted for age and sex, high ALT remained significantly associated with younger age, male sex, Asian ethnicity, increasing BMI, increasing waist circumference, decreasing central obesity, and undiagnosed diabetes. It was no longer significantly associated with alcohol consumption (Table 21).

In the univariate logistic regression model, high AST was significantly associated with male sex, the second and fourth quintiles of deprivation, increasing BMI, increasing waist circumference, lower central obesity in men, diagnosed or undiagnosed diabetes and alcohol consumption. When adjusted for age and sex, high AST remained significantly associated with male sex, the second and fourth quintiles of deprivation, increasing BMI, increasing waist circumference, lower central obesity in men, and diagnosed or undiagnosed diabetes. It was no longer significantly associated with alcohol consumption (Table 21).

Table 21: Univariate and age/sex adjusted logistic regression analysis. Binary outcome variables were ALT >40 yes/no; AST >40 yes/no.

		High ALT > 40 Weighted n = 327			**High AST > 40 Weighted n = 176**		
		Weighted n	Univariate OR (95%CI)	Age and sex adjusted OR (95%CI)	Weighted n	Univariate OR (95%CI)	Age and sex adjusted OR (95%CI)
Age	Age, years	3607	0.98 (0.98-0.99)**	0.99 (0.98-0.99)**	3425	0.99 (0.98-1.00)	0.99 (0.98-1.00)
Sex	Male	1755	Ref	Ref	1657	Ref	Ref
	Female	1851	0.32 (0.23-0.43)**	0.32 (0.24-0.44)**	1768	0.44 (0.29-0.65)**	0.44 (0.30-0.66)**
Ethnicity	White	3151	Ref	Ref	2990	Ref	Ref
	Black	95	0.77 (0.33-1.77)	0.70 (0.28-1.75)	85	0.94 (0.33-2.63)	0.92 (0.31-2.71)
	Asian	263	1.82 (1.13-2.94)*	1.68 (1.03-2.75)*	253	1.47 (0.71-3.05)	1.39 (0.66-2.92)
	Mixed/multiple/Other	92	1.25 (0.35-4.49)	0.99 (0.24-4.05	92	1.29 (0.27-6.24)	1.10 (0.19-6.34)
Index of multiple deprivation	Least deprived	697	Ref	Ref	650	Ref	Ref
	2nd	733	1.57 (0.98-2.54)	1.49 (0.93-2.40)	701	1.98 (1.24-3.18)**	1.90 (1.18-3.06)**
	3rd	813	1.15 (0.71-1.87)	1.01 (0.62-1.67)	783	1.16 (0.65-2.06)	1.06 (0.58-1.92)
	4th	684	1.34 (0.83-2.16)	1.12 (0.68-1.85)	642	2.15 (1.19-3.91)*	1.92 (1.08-3.40)*
	Most deprived	679	1.49 (0.92-2.42)	1.34 (0.81-2.21)	649	1.59 (0.86-2.93)	1.48 (0.78-2.80)
Education	NVQ4/NVQ5/degree or equivalent	1120	Ref	Ref	1067	Ref	Ref
	Below degree	1828	1.17 (0.83-1.65)	1.15 (0.82-1.63)	1724	1.33 (0.85-2.08)	1.32 (0.84-2.06)
	No qualification	657	0.97 (0.62-1.50)	1.26 (0.79-2.00	632	1.00 (0.54-1.85)	1.21 (0.62-2.35)
Smoking	Current	631	Ref	Ref	605	Ref	Ref
	Ex-regular	923	0.75 (0.48-1.16)	0.90 (0.59-1.38)	875	0.68 (0.39-1.19)	0.77 (0.44-1.35)
	Never	2053	0.76 (0.50-1.16)	0.88 (0.58-1.33)	1945	1.19 (0.71-1.99)	1.34 (0.79-2.25)
BMI	BMI continuous	3312	1.12 (1.09-1.15)**	1.15 (1.12-1.18)**	3260	1.07 (1.04-1.11)**	1.09 (1.05-1.12)**
	Normal	1208	Ref	Ref	1137	Ref	Ref
	Overweight	1203	2.69 (1.56-4.63)**	2.97 (1.70-5.19)**	1147	1.97 (1.14-3.42)*	2.03 (1.12-3.69)*
	Obese	851	6.26 (3.58-10.94)**	8.22 (4.65-14.5)**	810	3.05 (1.81-5.14)**	3.45 (1.99-5.99)**

		High ALT > 40 Weighted n = 327			High AST > 40 Weighted n = 176		
		Weighted n	Univariate OR (95%CI)	Age and sex adjusted OR (95%CI)	Weighted n	Univariate OR (95%CI)	Age and sex adjusted OR (95%CI)
Waist circumference	Male	1730	1.05 (1.03-1.06)**	1.07 (1.06-1.09)**	1631	1.03 (1.01-1.04)**	1.04 (1.02-1.06)**
	Female	1791	1.05 (1.03-1.07)**	1.05 (1.03-1.07)**	1708	1.03 (1.01-1.06)*	1.03 (1.01-1.06)**
Waist circumference (NICE categorisation)	Low (<94cm men, <80cm women)	1183	Ref	Ref	1115	Ref	Ref
	High (94-102 men, 80-88 women)	813	2.48 (1.42-4.33)**	3.60 (2.05-6.34)**	778	1.20 (0.65-2.22)	1.49 (0.82-2.71)
	Very high (>102 men, >88 women)	1260	3.55 (2.11-5.98)**	7.21 (4.16-12.49)**	1196	1.79 (1.01-3.19)*	2.71 (1.52-4.83)**
Central obesity		3256	0.77 (0.50-1.18)	0.25 (0.14-0.44)**	3090	0.90 (0.52-1.56)	0.46 (0.21-1.00)
Central obesity	Male	1612	0.16 (0.07-0.37)**	0.19 (0.08-0.45)**	1519	0.25 (0.08-0.78)*	0.30 (0.10-0.91)*
	Female	1644	0.43 (0.19-0.97)*	0.42 (0.19-0.94)*	1571	0.95 (0.35-2.61)	0.92 (0.32-2.63)
Diabetes	No diabetes	3212	Ref	Ref	3063	Ref	Ref
	Doctor diagnosed	235	1.54 (0.95-2.51)	2.02 (1.18-3.46)*	220	2.18 (1.12-4.24)*	2.72 (1.36-5.44)**
	undiagnosed	109	3.57 (2.12-6.00)**	5.11 (3.02-8.63)**	104	4.26 (2.25-8.07)**	5.58 (2.91-10.71)**
Alcohol	Total units/week	3577	1.01 (1.00-1.02)**	1.01 (1.00-1.01)*	3396	1.01 (1.00-1.01)**	1.01 (1.00-1.01)
Alcohol	None	597	Ref	Ref	565	Ref	Ref
	Low	2106	0.78 (0.52-1.16)	0.72 (0.48-1.07)	1997	0.78 (0.44-1.40)	0.74 (0.42-1.31)
	Intermediate	719	1.09 (0.70-1.71)	0.85 (0.54-1.33)	683	1.20 (0.59-2.47)	1.00 (0.49-2.04)
	High	155	1.73 (0.96-3.10)	1.53 (0.84-2.78)	151	1.63 (0.75-3.55)	1.46 (0.67-3.20)
Physical activity MVPA	Inactive	714	Ref	Ref	679	Ref	Ref
	Low or some activity	531	1.05 (0.59-1.84)	0.99 (0.56-1.73)	511	1.01 (0.51-2.00)	0.96 (0.49-1.90)
	Meets MVPA guidelines	2328	1.06 (0.72-1.57)	0.81 (0.54-1.22)	2202	1.10 (0.63-1.89)	0.90 (0.51-1.58)

* indicates significance at the 0.05 level ** indicates significance at the 0.01 level

MVPA = Moderate and Vigorous Physical Activity

In the univariate logistic regression model, high FIB-4 was significantly associated with increasing age, male sex, the second, third and fifth quintile of deprivation, no qualifications, increasing waist circumference in women, increasing central obesity overall and in men, diagnosed or undiagnosed diabetes and decreasing physical activity. In the age and sex adjusted model, high FIB-4 remained significantly associated with increasing age, male sex and the second and third quintiles of deprivation. The FIB-4 model was repeated excluding participants under 35years, as evidence suggests it is not discriminatory in this age group,[101] but this had no effect on the results (Table 22).

The regression results for high APRI are presented for completeness, although they may be of limited value due to the small number of participants who had a high APRI score (n=22). In the univariate logistic regression model, high APRI was significantly associated with increasing waist circumference in women. When adjusted for age and sex, high APRI was significantly associated with diagnosed diabetes and total alcohol consumption (Table 22).

Table 22: Univariate and age / sex adjusted logistic regression analysis. Binary outcome variables were FIB-4 >2.67 yes/no and APRI ≥1.0 yes/no.

		High FIB-4 >2.67 Weighted n = 85			**High APRI ≥ 1.0 Weighted n = 22**		
		Weighted n	Univariate OR (95%CI)	Age and sex adjusted OR (95%CI)	Weighted n	Univariate OR (95%CI)	Age and sex adjusted OR (95%CI)
Age	Age, years	3388	1.10 (1.08-1.11)**	1.10 (1.08-1.12)**	3389	0.99 (0.96-1.02)	0.99 (0.96-1.02)
Sex	Male	1641	Ref	Ref	1641	Ref	Ref
	Female	1747	0.61 (0.41-0.91)*	0.51 (0.34-0.78)**	1748	0.46 (0.20-1.10)	0.47 (0.20-1.10)
Ethnicity	White	2953	Ref	Ref	2954	Ref	Ref
	Black	85	1.50 (0.52-4.32)	2.58 (0.92-7.19)	85	No obs	No obs
	Asian	252	0.51 (0.16-1.60)	1.34 (0.40-4.53)	252	1.08 (0.24-4.82)	1.00 (0.21-4.68)
	Mixed/multiple/Other	92	0.32 (0.04-2.40)	0.85 (0.11-6.86)	92	No obs	No obs
Index of multiple deprivation	Least deprived	641	Ref	Ref	642	No obs	No obs
	2nd	694	0.45 (0.26-0.77)**	0.52 (0.29-0.92)*	694	Ref	Ref
	3rd	776	0.34 (0.17-0.66)**	0.46 (0.24-0.88)*	776	0.87 (0.16-4.66)	0.84 (0.15-4.73)
	4th	634	0.74 (0.42-1.30)	1.21 (0.69-2.12)	634	1.46 (0.33-6.51)	1.38 (0.27-7.00)
	Most deprived	643	0.37 (0.20-0.71)**	0.69 (0.36-1.32)	643	0.64 (0.13-3.22)	0.63 (0.12-3.49)
Education	NVQ4/NVQ5/degree or equivalent	1059	Ref	Ref	1059	Ref	Ref
	Below degree	1703	1.34 (0.76-2.37)	1.04 (0.57-1.91)	1703	0.98 (0.35-2.74)	0.97 (0.35-2.71)
	No qualification	623	4.14 (2.36-7.27)**	1.15 (0.63-2.09)	624	0.47 (0.11-1.92)	0.53 (0.11-2.45)
Smoking	Current	600	Ref	Ref	600	Ref	Ref
	Ex-regular	865	1.95 (0.99-3.86)	0.65 (0.32-1.31)	865	0.45 (0.10-1.98)	0.49 (0.10-2.44)
	Never	1923	1.32 (0.71-2.47)	0.83 (0.44-1.56)	1924	0.73 (0.24-2.26)	0.81 (0.25-2.58)
BMI	BMI continuous	3111	1.01 (0.97-1.04)	0.99 (0.94-1.03)	3111	1.02 (0.96-1.09)	1.03 (0.98-1.10)
	Normal	1127	Ref	Ref	1127	Ref	Ref
	Overweight	1134	1.46 (0.87-2.46)	1.01 (0.59-1.72)	1134	0.76 (0.21-2.70)	0.79 (0.23-2.80)
	Obese	804	1.24 (0.71-2.14)	0.91 (0.53-1.57)	804	0.91 (0.26-3.18)	1.02 (0.32-3.22)

		High FIB-4 >2.67 Weighted n = 85			High APRI ≥ 1.0 Weighted n = 22		
		Weighted n	Univariate OR (95%CI)	Age and sex adjusted OR (95%CI)	Weighted n	Univariate OR (95%CI)	Age and sex adjusted OR (95%CI)
Waist circumference	Male	1615	1.01 (0.99-1.03)	0.98 (0.95-1.01)	1615	1.00 (0.95-1.06)	1.02 (0.97-1.06)
	Female	1688	1.03 (1.02-1.05)**	1.02 (0.99-1.04)	1688	1.06 (1.01-1.10)*	1.06 (1.02-1.10)
Waist circumference (NICE categorisation)	Low (<94cm men, <80cm women)	1102	Ref	Ref	1102	Ref	Ref
	High (94-102 men, 80-88 women)	771	1.10 (0.60-2.01)	0.53 (0.28-1.04)	771	0.38 (0.09-1.65)	0.43 (0.11-1.62)
	Very high (>102 men, >88 women)	1183	1.60 (0.96-2.67)	0.70 (0.44-1.14)	1183	0.59 (0.22-1.60)	0.73 (0.35-1.53)
Central obesity		3056	3.88 (2.04-7.37)**	1.42 (0.70-2.89)	3056	1.23 (0.33-4.61)	0.93 (0.21-4.17)
Central obesity	Male	1504	6.83 (2.94-15.87)**	2.39 (0.83-6.89)	1504	1.32 (0.16-10.59)	1.71 (0.24-12.09)
	Female	1552	2.01 (0.83-4.89)	0.88 (0.34-2.27)	1552	0.42 (0.05-3.67)	0.40 (0.04-3.64)
Diabetes	No diabetes	3045	Ref	Ref	3046	Ref	Ref
	Doctor diagnosed	219	2.81 (1.47-5.38)**	1.16 (0.57-2.36)	219	3.87 (1.17-	4.98 (1.60-15.53)**
	undiagnosed	104	3.64 (1.78-7.43)**	1.26 (0.57-2.76)	104	3.13 (0.55-17.64)	4.19 (0.70-25.15)
Alcohol	Total units/week	3358	1.00 (1.00-1.01)	1.01 (1.00-1.01)	3359	1.01 (1.00-	1.01 (1.00-1.02)**
Alcohol	None	562	Ref	Ref	563	Ref	Ref
	Low	1974	0.64 (0.38-1.07)	0.74 (0.42-1.30)	1974	0.66 (0.18-2.43)	0.63 (0.18-2.21)
	Intermediate	674	0.75 (0.39-1.42)	0.74 (0.36-1.51)	974	1.13 (0.29-4.39)	0.96 (0.26-3.57)
	High	149	1.16 (0.44-3.06)	1.37 (0.49-3.83)	149	3.10 (0.88-11.01)	2.80 (0.76-10.30)
Physical activity MVPA	Inactive	666	Ref	Ref	667	Ref	Ref
	Low or some activity	510	0.53 (0.30-0.93)*	0.81 (0.44-1.48)	510	0.58 (0.14-2.52)	0.55 (0.13-2.40)
	Meets MVPA guidelines	2179	0.34 (0.22-0.54)**	0.84 (0.52-1.35)	2179	0.84 (0.30-2.34)	0.69 (0.27-1.73)

* indicates significance at the 0.05 level ** indicates significance at the 0.01 level

MVPA = Moderate and Vigorous Physical Activity

The age and sex adjusted logistic regression model, for obesity, alcohol and diabetes liver disease risk factors only, are summarised in Table 23. High ALT was significantly more likely with increasing BMI, increasing waist circumference, diagnosed or undiagnosed diabetes and increasing total alcohol consumption. The increased chance of a High ALT per unit increase in total alcohol consumption was very small (0.01 times more likely) and high ALT was not significantly associated with alcohol consumption when categorised.

High AST was significantly more likely with increasing BMI, very high waist circumference and diagnosed or undiagnosed diabetes. High AST was not significantly associated with alcohol consumption.

High FIB-4 was not significantly associated with any risk factors. High APRI was significantly associated with doctor diagnosed diabetes and increasing total alcohol consumption per week. The increased chance of a high APRI per extra unit of alcohol consumed per week was very small (0.01 times more likely) and high APRI was not significantly associated with alcohol consumption when categorised.

Table 23: Age and sex adjusted logistic regression analysis for alcohol and obesity related risk factors. Binary outcome variables were ALT>40 yes/no, AST>40 yes/no, FIB-4>2.67 yes/no, APRI≥1.0 yes/no.

		High ALT >40 Weighted n = 327		**High AST>40 Weighted n = 176**		**High FIB-4 >2.67 Weighted n = 85**		**High APRI ≥ 1.0 Weighted n = 22**	
		Weighted n	Age and sex adjusted OR (95%CI)	Weighted n	Age and sex adjusted OR (95%CI)	Weighted n	Age and sex adjusted OR (95%CI)	Weighted n	Age and sex adjusted OR (95%CI)
BMI	BMI continuous	3312	1.15 (1.12-1.18)**	3144	1.09 (1.05-1.12)**	3111	0.99 (0.94-1.03)	3111	1.03 (0.98-1.10)
	Normal <25		Ref		Ref		Ref		Ref
	Overweight 25 to <30		2.97 (1.70-5.19)**		2.03 (1.12-3.69)*		1.01 (0.59-1.72)		0.79 (0.23-2.80)
	Obese ≥ 30		8.22 (4.65-14.5)**		3.45 (1.99-5.99)**		0.91 (0.53-1.57)		1.02 (0.32-3.22)
Waist circumference (NICE categorisation)	Waist circumference continuous	3521	1.06 (1.05, 1.07)**	3340	1.04 (1.02, 1.05)**	3303	1.10 (1.08, 1.12)**	3303	1.03 (1.00, 1.06)*
	Low (<94cm men, <80cm women)		Ref		Ref		Ref		Ref
	High (94-102 men, 80-88 women)		3.60 (2.05-6.34)**		1.49 (0.82-2.71)		0.53 (0.28-1.04)		0.43 (0.11-1.62)
	Very high (>102 men, >88 women)		7.21 (4.16-12.49)**		2.71 (1.52-4.83)**		0.70 (0.44-1.14)		0.73 (0.35-1.53)
Diabetes	No diabetes	3555	Ref	3387	Ref	3369	Ref	3370	Ref
	Doctor diagnosed		2.02 (1.18-3.46)*		2.72 (1.36-5.44)**		1.16 (0.57-2.36)		4.98 (1.60-15.53)**
	undiagnosed		5.11 (3.02-8.63)**		5.58 (2.91-10.71)**		1.26 (0.57-2.76)		4.19 (0.70-25.15)
Alcohol	Total units/week	3577	1.01 (1.00-1.01)*	3396	1.01 (1.00-1.01)	3358	1.01 (1.00-1.01)	3359	1.01 (1.00-1.02)**
	None		Ref		Ref		Ref		Ref
	Low		0.72 (0.48-1.07)		0.74 (0.42-1.31)		0.74 (0.42-1.30)		0.63 (0.18-2.21)
	Intermediate		0.85 (0.54-1.33)		1.00 (0.49-2.04)		0.74 (0.36-1.51)		0.96 (0.26-3.57)
	High		1.53 (0.84-2.78)		1.46 (0.67-3.20)		1.37 (0.49-3.83)		2.800.76-10.30)

* Indicates significance at the 0.05 level ** indicates significance at the 0.01 level

3.4.4.2 Linear regression models

Results from linear regression modelling were broadly similar and are shown in full in Appendix B. The age and sex adjusted linear regression models for obesity, alcohol and diabetes liver disease risk factors only, are summarised in Table 24. The age and sex adjusted model showed a significant relationship between ALT and BMI, waist circumference and total weekly alcohol consumption. For every unit increase in BMI, ALT increased by 0.86 IU/L. R squared for the model was 0.172 indicating that 17.2% of the variation in ALT can be explained by the model including BMI, adjusted for age and sex. For every unit increase in waist circumference, ALT increased by 0.35 IU/L. R squared for the model was 0.173 indicating that 17.3% of the variation in ALT can be explained by the model including waist circumference, adjusted for age and sex. For every extra unit of alcohol consumed per week, ALT increased by 0.04 IU/L. R squared for the model was 0.081 indicating that 8.1% of the variation in ALT can be explained by the model including total weekly alcohol consumption, adjusted for age and sex.

Increasing ALT was significantly associated with overweight or obese BMI, high or very high waist circumference, diagnosed or undiagnosed diabetes and high alcohol consumption.

The age and sex adjusted model showed a significant relationship between AST and BMI, waist circumference and total weekly alcohol consumption. For every unit increase in BMI, AST increased by 0.21 IU/L. R squared for the model was 0.044 indicating that 4.4% of the variation in AST can be explained by the model including BMI, adjusted for age and sex. For every unit increase in waist circumference, AST increased by 0.07 IU/L. R squared for the model was 0.040 indicating that 4.0% of the variation in AST can be explained by the model including waist circumference, adjusted for age and sex. For every extra unit of alcohol consumed per week, AST increased by 0.04 IU/L. R squared for the model was 0.035 indicating that 3.5% of the variation in AST can be explained by the model including total weekly alcohol consumption, adjusted for age and sex.

Increasing AST was significantly associated with overweight or obese BMI, high or very high waist circumference, undiagnosed diabetes and high alcohol consumption.

The age and sex adjusted model showed a significant relationship between FIB-4 and BMI, waist circumference and total weekly alcohol consumption. For every unit increase in BMI, FIB-4 decreased by 0.01. R squared for the model was 0.493 indicating that 49.3% of the variation in FIB-4 can be explained by the model including BMI, adjusted for age and sex. For every unit increase in waist circumference, FIB-4 decreased by 0.004 ($p<0.001$). R squared for the model was 0.486 indicating that 48.6% of the variation in FIB-4 can be explained by the model including waist

circumference, adjusted for age and sex. For every unit increase in total weekly alcohol consumption, FIB-4 increased by 0.001 (p=0.047). R squared for the model was 0.485 indicating that 48.5% of the variation in FIB-4 can be explained by the model including total weekly alcohol consumption, adjusted for age and sex.

Decreasing FIB-4 was significantly associated with overweight or obese BMI and high or very high waist circumference.

The age and sex adjusted model showed a significant relationship between APRI and BMI, waist circumference and total weekly alcohol consumption. For every unit increase in BMI, APRI increased by 0.001 (p=0.012). R squared for the model was 0.053 indicating that 5.3% of the variation in APRI can be explained by the model including BMI, adjusted for age and sex. For every unit increase in waist circumference, APRI increased by 0.001 (p=0.024). R squared for the model was 0.0546 indicating that 5.5% of the variation in APRI can be explained by the model including waist circumference, adjusted for age and sex. For every unit increase in total weekly alcohol consumption, APRI increased by 0.001 (p=0.002). R squared for the model was 0.056 indicating that 5.6% of the variation in APRI can be explained by the model including total weekly alcohol consumption, adjusted for age and sex.

Increasing APRI was significantly associated with obese BMI and high alcohol consumption.

Table 24: Age and sex adjusted linear regression analysis for alcohol and obesity related risk factors. ALT, AST, FIB-4 and APRI.

		ALT		AST		FIB-4		APRI	
		Weighted n	Age and sex adjusted Coefficient (95%CI)	Weighted n	Age and sex adjusted Coefficient (95%CI)	Weighted n	Age and sex adjusted Coefficient (95%CI)	Weighted n	Age and sex adjusted Coefficient (95%CI)
BMI	BMI continuous	3312	0.86 (0.70, 1.01)**	3144	0.21 (0.13, 0.29)**	3111	-0.01 (-0.01, -0.01)**	3111	0.00 (0.00, 0.00)*
	Normal <25		Ref		Ref		Ref		Ref
	Overweight 25 to <30		4.87 (3.76, 5.97)**		1.16 (0.36, 1.97)**		-0.07 (-0.11, -0.04)**		0.01 (-0.00, 0.02)
	Obese ≥ 30		11.17 (9.21, 13.13)**		2.98 (2.05, 3.91)**		-0.11 (-0.15, -0.07)**		0.02 (0.00, 0.03)**
Waist circumference (NICE categorisation)	Waist circumference continuous	3521	0.35 (0.30, 0.41)**	3340	0.07 (0.04, 0.11)**	3303	-0.004 (-0.01, -0.00)**	3303	0.00 (0.00, 0.00)*
	Low (<94cm men, <80cm women)		Ref		Ref		Ref		Ref
	High (94-102 men, 80-88 women)		5.35 (3.93, 6.78)**		1.21 (0.12, 2.30)*		-0.07 (-0.11, -0.04)**		0.01 (-0.01, 0.02)
	Very high (>102 men, >88 women)		10.23 (8.44, 12.03)**		1.94 (1.00, 2.88)**		-0.14 (-0.18, -0.11)**		0.01 (-0.00, 0.02)
Diabetes	No diabetes	3555	Ref	3387	Ref	3369	Ref	3370	Ref
	Doctor diagnosed		3.40 (0.89, 5.92)**		0.11 (-1.75, 1.96)		-0.04 (-0.15, 0.06)		0.01 (-0.02, 0.04)
	undiagnosed		10.81 (5.70, 15.91)**		4.57 (1.44, 7.71)**		-0.05 (-0.20, 0.09)		0.06 (-0.01, 0.14)
Alcohol	Total units/week	3577	0.04 (0.01, 0.07)**	3396	0.04 (0.02, 0.06)**	3358	0.001 (0.00, 0.00)*	3359	0.00 (0.00, 0.00)**
	None		Ref		Ref		Ref		Ref
	Low		-0.93 (-2.65, 0.79)		-0.12 (-1.10, 0.86)		0.00 (-0.04, 0.05)		-0.01 (-0.02, 0.01)
	Intermediate		0.23 (-1.87, 2.33)		0.80 (-0.49, 2.08)		-0.01 (-0.06, 0.05)		-0.00 (-0.02, 0.02)
	High		2.57 (0.07, 5.08)*		3.60 (1.70, 5.50)**		0.12 (-0.02, 0.27)		0.050.01, 0.09)**

** indicates significance at the 0.05 level ** indicates significance at the 0.01 level

3.5 Discussion

3.5.1 Risk factors

Multiple risk factors for liver disease were present in more than one quarter of participants in this general population sample (28.4%) and were nearly twice as common in men, compared to women. Many sociodemographic factors were significantly associated with multiple risk factors. Multiple risk factors were present in a significantly higher proportion of participants of white ethnicity, those aged more than 55 years, those with no educational qualifications and in those who were ex-smokers. Half of this general population sample had risk factors for NAFLD.

The proportion of participants within risk factor categories varied significantly across all sociodemographic variables. NAFLD risk was the only category which was more common in females than males. The distribution of those with risk factors for BAFLD, among socioeconomic variables, was very different from those with risk factors for NAFLD. Trends were in opposite directions for BAFLD and NAFLD within employment, index of multiple deprivation and educational attainment. These findings support the proposal that those with risk factors for BAFLD are a distinct group, with distinct characteristics compared to those at risk of NAFLD or ALD. Understanding this is important in order to implement primary prevention measures, and for targeted prevention strategies to be effective.

According to our definition, 12.2% of the sample (17.3% of men) were at risk of BAFLD (**B**oth **A**lcoholic and **F**atty **L**iver **D**isease). This group were distinct from those at risk of NAFLD, as in addition to being overweight or obese they had higher than recommended alcohol consumption (but below harmful). This group are at significantly increased risk of liver disease, due to the multiplicative risk from both increased alcohol consumption and increased BMI which was demonstrated in chapter two, and has been reported elsewhere.[59 102] This is a high proportion of the population, and the prevalence of BAFLD may be under-reported, due to inaccuracy in self-reporting of alcohol consumption.

The EASL–EASD–EASO Clinical Practice Guidelines state that the interaction between moderate alcohol intake and metabolic risk factors should always be considered.[103] Although the co-existence of NAFLD and ALD is acknowledged, this multiplicative risk is rarely reflected in clinical pathways in the UK.[73 103] The population at risk of BAFLD are often missed using current diagnostic and referral criteria. For example, NAFLD referral pathways typically target those drinking less than 14 units of alcohol per week whereas ARLD pathways target those drinking harmful quantities of alcohol (>35 units/week for women and >50 units/week for men).[58 104 105] There are

few, if any, pathways which target the BAFLD group. In the definition of BAFLD proposed here, those who drink harmful quantities of alcohol and are also overweight or obese have been excluded. Although these people are at high risk of liver disease, they meet the criteria for ARLD pathways and should therefore be identified and referred through these.

It could be argued that all those who are overweight/obese and consume above recommended limits of alcohol should be included in the definition of BAFLD. Clarity on this could be achieved by a re-structuring of ICD-10 disease codes. However the real need for highlighting the BAFLD group is to correctly identify those at risk, to intervene early, since cirrhosis is the same regardless of aetiology. Education about risk factors should focus on the multiplicative risk of alcohol and increased BMI, for all levels of alcohol consumption, and the term BAFLD could be used here if helpful. Pathways into care should focus on the BAFLD group as a currently missed cohort of high risk patients. Definitions of BAFLD, ARLD and NAFLD may vary locally in the context of pathways. The important need is to ensure that patients at risk of BAFLD are included in the risk assessment part of pathways, and that their increased risk is acknowledged in risk stratification strategies.

Alcohol and obesity are modifiable risk factors and therefore present an opportunity for early intervention and prevention of disease progression. Understanding of the aetiology of liver disease amongst the general population is poor[61] and in this sample awareness of risk factors for liver disease was very low. Only 4.4% of the sample reported ever being told they were at risk of liver disease, despite 89% having at least one risk factor and 28% having two or more risk factors. Awareness of cardiovascular risk factors in the general population is significantly higher than this,[106 107] suggesting that improvement could be achieved.

3.5.2 Non-invasive markers of liver disease

The HSE 2016 was the first, and currently only, time that liver blood tests have been performed in a large sample, representative of the general population of England living in private households. Abnormal liver blood test results (AST or ALT) were found in 10.9% of the study population. This is approximately half the prevalence found in previous estimates, which were based on patients who had already had liver blood tests performed in primary care for any reason.[108]

Using standard liver blood tests and fibrosis scores (non-invasive markers), we found large variations in the proportion of the population who had a high test result. Non-invasive markers have been developed in populations with specific liver pathology and it is important to note that they have not been validated in general populations.[24 91 97 109] The interpretation of these markers

of liver disease in general populations is not well understood. There is a clear need for development of better markers or risk indices, as up to 60-70% of liver deaths are not associated with high fibrosis scores (APRI, NAFLD fibrosis score, FIB-4, Forns score - over 23 years follow up of the NHANES cohort).[73 98] However, it is also important to advance knowledge about the correct interpretation of currently available tests and markers in the general population, as these are often used to assess and risk stratify patients.

The AST:ALT ratio identified more than 70% of the general population as having a high score. As a raised AST:ALT ratio automatically triggers a high BARD score, the BARD score also becomes ineffective in this setting. An important point is that 69% of the population had a high AST:ALT ratio but had individual AST and ALT results within the normal range. Current British Society of Gastroenterology (BSG) guidelines on initial investigation for potential liver disease, state that "the utility of the AST:ALT ratio in adults persists even if both values are within the normal reference interval". The results presented here would strongly suggest that this is not the case. The AST:ALT ratio should therefore be used with caution in general population settings. Hepatologists must communicate criteria around its use clearly, in order to avoid an excessive number of referrals for further investigation.

The AST:ALT ratio has been shown to have a Negative Predictive Value (NPV) of 93%[24] in patients with NAFLD (although this was in a selected population at a tertiary referral centre), and it has been recommended by the Lancet Commission[2 110] to rule out significant fibrosis in NAFLD patients in primary care. It is important to remember that NAFLD patients are not the same as the general population, as the results of this thesis clearly show. When assessing the value of non-invasive markers of liver disease, to avoid errors due to spectrum bias, markers must be evaluated in the broadest range of patients in which they will be used – in this case the general population.

The FIB-4 score was highly age dependent, as might be expected since it contains age in its formula. Age-specific cut offs for FIB-4 in NAFLD patients have been suggested[101] but there is no guidance for general population settings. Evaluation of a new pathway to triage NAFLD patients in primary care using FIB-4, showed that using the suggested age-specific cut offs would have resulted in a reduction of 29 referrals, but 12 cases with advanced fibrosis would have been missed[111]. The correct approach remains unclear. In this sample, when adjusted for age and sex, a high FIB-4 score was not significantly associated with any obesity or alcohol risk factors. This did not change if the age-specific cut offs recommended for NAFLD patients were applied. There is a real need for better understanding of FIB-4 performance in general population settings, as it is currently used in many primary care risk algorithms.

The proportion with a high score for liver blood tests and fibrosis scores varied between different 'at risk' populations. This variation was not consistent across tests and scores, suggesting they may be sensitive to different risk factors. Within each risk factor category, the proportion of males with a high ALT was much higher than that for females. This was not the case for FIB-4 or APRI. Some laboratories use different cut offs for males and females for ALT but the HSE laboratory used the same cut off for both sexes, which may explain the finding. In addition, liver blood tests and fibrosis scores often did not identify the same individuals as having a 'high' result. This suggests a single test used in isolation is unlikely to be reliable. Approaches using combinations of fibrosis scores, have been shown to be effective[111 112] and the addition of further risk factor information to these models may enhance their ability to correctly identify those most at risk. There is a need to achieve a balance between identifying all those at risk but who can be safely managed in primary care, whilst referring the minority who require specialist input to secondary care.

3.5.3 Strengths and limitations

This study used a large, methodologically robust survey, representative of the general population of England living in private households. The results may not represent those in hospital, living in institutions or homeless people. The survey used standardised protocols by trained interviewers and nurses. All blood samples were tested in the same laboratory. We used appropriate complex survey data techniques to account for survey design and non-response. Data were available on waist circumference, as well as BMI, which may be better in assessing risk of NAFLD.[113] The survey is cross sectional and therefore no causal relationships can be inferred from the associations identified. BMI was measured but alcohol data was self-reported and may be underestimated. Ethnic specific cut offs for BMI and waist circumference categories were not used. Diabetes was not separated in to type 1 and type 2. Age was only available in five year categories. AST and ALT thresholds are lab-specific, so alternative thresholds cannot be explored. There was no virology performed, so we cannot determine or adjust for the proportion of the population who have viral hepatitis, although prevalence is low in the UK.

The main limitation of this study was no data on liver disease outcomes, or procedural measures of fibrosis such as transient elastography. The correct interpretation of non-invasive fibrosis markers in the general population is unknown and we cannot draw conclusions from these data about liver disease outcomes. However, associations between risk factors and liver disease outcomes have been demonstrated,[73] as have associations between liver fibrosis scores and liver

disease outcomes.[98] NHANES III was a cross-sectional survey very similar in design to the HSE, conducted in the USA. In the NHANES general population cohort, over 23 years of follow up, FIB-4>2.67 and APRI >0.5 were associated with significantly increased risk of liver disease mortality.[98] The proportion of the general population with high FIB-4 and high APRI in this HSE survey was very similar to that found in NHANES III, which gives confidence that these are robust estimates of prevalence in the general population.

We were unable to calculate certain fibrosis tests, such as the ELF® test[114] and NAFLD fibrosis score. ELF® is currently recommended by the National Institute for Health and Care Excellence in the UK (NICE) to detect fibrosis in patients with NAFLD in primary care.[104]

The absolute number of participants in this sample with high scores for Fib-4 and APRI was small. The power of statistical testing was therefore limited, particularly for APRI.

3.5.4 Further research

Liver disease often presents late, with irreversible fibrosis or cirrhosis and poor outcomes.[115] There is a need for better ways to detect significant fibrosis in general population settings.[116 117] In future research, testing could be performed in a general population setting using a wider range of fibrosis scores, to better understand the triangulation between risk factors for liver disease, liver blood tests/fibrosis scores and liver disease outcomes. Accurate population-based measures of all three are needed. Interestingly, this study found that awareness of liver disease risk in the population was highest in those with diagnosed diabetes. This would be worth exploring further, to maximise opportunities for joint initiatives and collaboration across specialties.

As routine liver blood tests are not sensitive or specific for detecting fibrosis, cost-effectiveness analyses assessing more expensive but more accurate tests, such as Fibroscan or ELF®, are needed. Targeting these tests for those at highest risk could be a cost effective strategy, but would rely on the establishment of more accurate risk stratification.

3.5.5 Conclusion

Modifiable risk factors for liver disease were very common in this general population sample, fitting the model of Geoffrey Rose's 'sick' population. However, personal awareness of risk was low. Half of this general population sample were at risk of NAFLD and a further 12% had a

combination of alcohol and obesity risk factors, putting them at risk of BAFLD. Within the general population of the UK, primary prevention strategies should occur at both population level (89% of the sample had at least one risk factor) and targeted at the highest risk, who will experience the most harm (4.3% high risk alcohol consumption, 1.5% high risk alcohol consumption and overweight/obese). Risk factors were strongly linked to sociodemographic and socioeconomic factors, suggesting that further segmentation of those most at risk is possible.

Abnormal liver blood tests were half as common in the general population (10.9%) than in previous estimates, which were from patients who had had liver blood tests taken in primary care for other reasons.[108] This highlights the point that the general population are different to both primary care and secondary care patients. This should be remembered when tests are being validated – tests to be used in general population settings must be validated in such to avoid errors due to spectrum bias. Commonly used non-invasive markers for liver disease showed large variation in positivity in the general population and concordance between tests was low. Contrary to current guidelines, the AST:ALT ratio was not discriminatory in this general population setting, without further qualifications around its use. Non-invasive markers differed significantly in their performance between risk factor categories. More evidence on the interpretation of non-invasive markers of liver disease in the general population is needed. For example from studies in general population settings which can validate the performance of non-invasive markers against liver disease outcomes measures.

The current classification of 'alcoholic' and 'non-alcoholic' liver disease means that an estimated 12% of the population who have both alcohol and obesity related risk factors, may be missed in risk assessment and clinical care. The size of this proportion of the general population, at increased risk of liver disease, demonstrates the need for clustering of risk factors to be reflected in risk stratification and care pathways.

3.6 Summary and next steps

This analysis has described the distribution of risk factors for liver disease among the general population of England, and their association with sociodemographic and socioeconomic factors. It has also described the distribution of some commonly used non-invasive markers of liver disease among the general population, and within specific risk categories. Associations between non-invasive markers for liver disease and risk factors have also been explored and described.

This analysis has shown that the vast majority of the general population had at least one risk factor for liver disease, and more than one quarter had multiple risk factors. Nearly two thirds of the population were overweight or obese, and nearly one quarter reported drinking alcohol above the recommended limits. These risk factors for liver disease were found in combination, in 16% of the population.

This group are at significantly increased risk of ALD and BAFLD, from the multiplicative effects of alcohol consumption and increased BMI. Alcohol damages the liver directly, but it also contributes calories to the diet. Alcoholic drinks can have a high calorie content, which could compound direct damage from alcohol by contributing to increased BMI.

In the next chapter, data from the National Diet and Nutrition Survey are analysed to explore the relationship between calories from alcohol and BMI.

Chapter 4: Alcohol calories and obesity: analysis of the National Diet and Nutrition Survey

4.1 Research objectives

1. To describe the pattern of alcohol consumption and calories from alcohol, in those who are overweight or obese in a UK general population sample.

2. To explore how calories from alcoholic beverages may vary across sociodemographic and socioeconomic factors, and by BMI categories.

4.2 Background

The prevalence of obesity in the UK has increased year on year since at least the 1970's. If the current trend continues, by 2030 41-48% of men and 35-43% of women in the UK population will be obese.[118] There is a substantial obesity-attributable disease burden in the UK from cardiovascular disease, diabetes, some cancers and fatty liver disease.[119]

Existing evidence suggests an association between alcohol and obesity.[120-123] The nature of this association is, however, less clear. The association seems to be non-linear in nature and is complex. It is influenced by a wide range of factors such as drinking pattern, type of alcoholic beverage consumed, gender, body weight, genes and physical activity.[120-122] Alcohol contains 7.1 kilocalories per gram, second only to fat, and calories from alcohol are metabolised in preference to those from fat or carbohydrate.[120-122 124] Research has shown that alcohol calories are consumed in addition to food calories, not replacing them.[122 125 126] There may also be an increase in food calorie intake, as a result of alcohol consumption.[120 122 125 126] As obesity levels continue to rise in the UK, with a disproportionate rise predicted for men[118], it is important to understand what contribution alcohol consumption makes to weight gain and in whom.

Researchers have called for further studies looking at alcohol in the context of wider lifestyle choices.[125] Better understanding of the role that calories from alcohol play in overall diet, may help with recommendations to reduce risk of liver disease in those who are overweight or obese. Data from the National Dietary and Nutrition Survey Rolling Programme (NDNS RP) provide a unique opportunity to describe the epidemiology of overweight and obesity in the UK in relation to alcohol consumption and calories from alcohol, with the ability to explore and adjust for important covariates such as physical activity and sociodemographic factors.

4.3 Methods

4.3.1 Sample, setting and measurements

The NDNS RP is a rolling, annual cross-sectional survey in a nationally representative sample of the general population, aged 18 months or older, living in private households in the UK. Participants were interviewed in their own home and then completed a self-reported food and beverage diary. A nurse visited two to eight weeks later, to take physical measurements including height and weight. Full details of the methods used in the survey are published and not reproduced here.[127-130] Nine years of data from 2008 –2017 were pooled (adults n=7112). Participants were excluded if they were underweight (BMI<18.5, n=111). Participants were excluded if they reported drinking alcohol previously, but having stopped. This was due to the increased likelihood of previous alcoholism or serious illness in this group (n=403).[69 131] One participant was excluded due to their age being recorded differently across the different NDNS datasets. Other errors may therefore have been present in this participant's data. After exclusions 6.597 adult participants were included in the analysis (Figure 24).

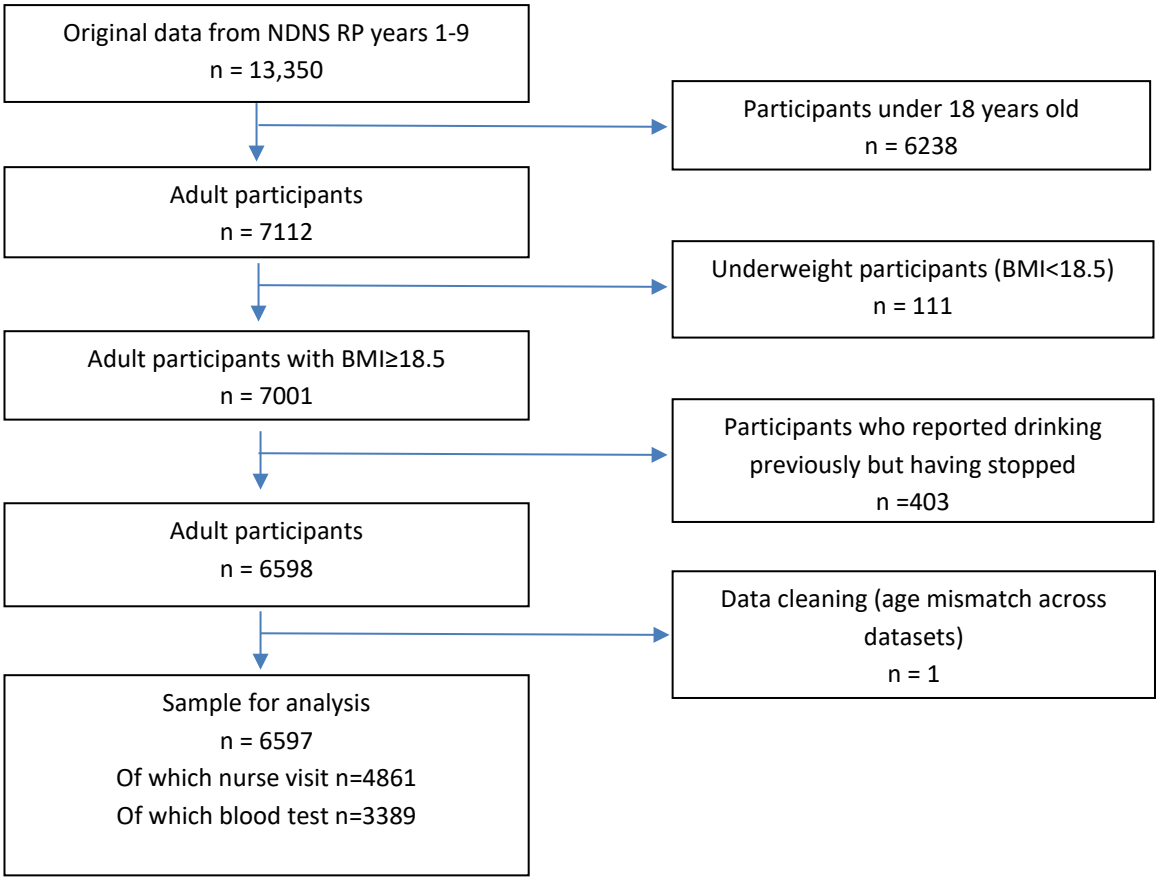


Figure 25: Data flow diagram showing derivation from the NDNS RP

4.3.2 Dataset

Data from the NDNS RP are available with no charge via the UK Data Service.[132] Datasets are provided separately by survey year, or group of years, and by the type of data collected. Datasets used in this analysis were from years one to nine of the survey.

BMI was calculated from height and weight measured during the nurse visit. BMI data were re-categorised as: healthy weight (>=18.5 to <25 kg/m^2), overweight (25 to <30 kg/m^2) and obese (≥30 kg/m^2). Ethnicity data in five categories were re-categorised as White or other. Education data were re-categorised as finishing at 18 years or under, or 19 years or older. Employment was derived by re-categorising the NS-SEC data in to the NS-SEC three class categorisation[133 134]. Smoking was categorised as current/never/ex-smoker. Physical activity was measured as time spent in moderate or vigorous exercise using the Recent Physical Activity Questionnaire (RPAQ) – data available from year two onwards (n=4593).

4.3.3 Alcohol data

Data about alcohol consumption were provided in several different forms. The questionnaire asked about alcohol consumption in different ways, designed to reflect average consumption over 12 months, and binge drinking on any one day. The food and beverage diary recorded by participants included all alcohol consumption.

Discrepancies were found in the answers given to different alcohol consumption questions, as well as discrepancies between answers to the alcohol consumption questions and recorded diary consumption. Without further information it would have been inaccurate to categorise participants as 'drinkers' or 'non-drinkers', so this was not attempted. Drinking frequency over the last 12 months, as reported in the interview, was investigated. Alcohol calories, as reported in the diary data, were separately investigated.

The following groups of alcohol consumers were derived from the available data, and analysis focused on each of these groups in turn:

Table 25: Groups of alcohol consumers derived from the NDNS data

Alcohol consumption group	Data derived from
Frequency of alcohol consumption over the past 12 months	Self-reported questionnaire
Binge drinking	Self-reported questionnaire
Drank any alcohol during four day diary	Four day food and beverage diary
Estimate of weekly alcohol consumption (subgroup)	Four day food and beverage diary

The following sections describe the methods used to derive alcohol consumption in each of the groups in Table 25.

4.3.3.1 Frequency of reported alcohol consumption over the past 12 months and binge drinking

Participants aged 18-24 years were offered the option of using a self-completion booklet, to answer questions about alcohol consumption (Appendix C1). Adults who did not choose the self-completion booklet, or who were aged 25 years or older, were asked questions about their alcohol consumption by the interviewer (Appendix C2). Questions asked how often participants had consumed alcohol over the past 12 months. Answers were multiple choice:

1. Almost every day
2. Five or six days per week
3. Three or four days per week
4. Once or twice per week
5. Once or twice per month
6. Once every couple of months
7. Once or twice per year
8. Not at all in the last 12 months

For the purpose of this analysis, these data were re-categorised to try and reflect UK recommended alcohol consumption guidelines: [68]

- At least five days per week (approximation to above recommended UK limits)
- Once to four times per week (approximation to within recommended UK limits)
- Once per month to once per year (infrequent)
- Not at all

Binge drinking

Further questions in the self-completion booklet or interview asked whether the participant had drunk alcohol on any day in the previous week. If they had, they were asked on how many days in the last week they had drunk alcohol. They were then asked to think about the day on which they drank the most alcohol, and to report all alcohol consumed on this day. This was reported by drink type:

- Normal strength beer, lager, stout cider or shandy (less than 6% alcohol)
- Strong beer, lager, stout or cider (6% alcohol or more)
- Spirits or liqueurs
- Sherry or martini
- Wine
- Alcoholic soft drinks or pre-mixed alcoholic drinks
- Other

Participants were also asked to record how much of each type of alcohol they consumed on that day (Appendix C.1). Units of alcohol consumed were calculated from these data and reported in the NDNS dataset. For this analysis, binge drinking was classified as reported drinking more than six units on heaviest drinking day for women, more than eight units for men.[135]

4.3.3.2 Alcohol consumed during four day diary

Self-reported food diaries were completed over three (n=140, 2.1%) or four (n=6457, 97.9%) days. Participants were asked to write down the time of each eating or drinking occasion that occurred during the duration of the diary. They were asked to record foods and beverages with as much detail as possible, including brand names and portion sizes. Guidance on glass sizes (Appendix C4) and an example completed diary page (Appendix C3) were provided. For this part of the analysis, participants were categorised depending on whether they had consumed any alcohol during their diary period, or not. This was not defining them as 'drinkers' or 'non-drinkers', merely describing the alcohol related activity reported in their diary. For comparisons to be valid, only those completing a four day diary were included in this part of the analysis.

Calories from food and beverage intake recorded were calculated and reported in the NDNS dataset as 'alcohol calories' and 'food calories'. Information on total calorie consumption was also provided. 'Alcohol calories' did not include calories from alcohol used for cooking. A new variable, 'alcohol beverage calories', was created to capture all calories associated with alcoholic drinks, for example from 'mixers' consumed with alcohol e.g. tonic water. This variable was formed by adding calories from any soft drinks consumed at exactly the same time as alcohol in the diary, to the alcohol calories. Alcohol free beer/wine were not included in alcohol beverage calories.

4.3.3.3 Subgroup with accurate estimate of weekly alcohol consumption

It was considered useful to be able to describe weekly alcohol intake, for two reasons. Firstly, UK alcohol consumption guidelines are given per week and so a weekly estimate would be needed in order to explore whether participants were drinking within recommended limits. Secondly, alcohol consumption behaviour is likely to vary across the week. The variation may differ for individuals depending on factors such as working patterns. Hence, assumptions cannot be made about weekly consumption from a four day diary and data cannot be reasonably extrapolated.

In order to estimate total weekly alcohol calories, a subgroup of alcohol consumers was defined (n=1925). The subgroup included participants whose recorded alcohol consumption in the diary exactly matched the frequency of consumption they reported in the questionnaire. Their diary consumption could therefore be taken as their weekly consumption, or multiplied up where appropriate. Participants reporting alcohol consumption less than once per week were not

included in the sub group. Criteria for entry to the subgroup are show in Table 26. Only participants who completed four diary days were included.

Table 26: Method for creation of a sub-group in which interview reported alcohol consumption matched diary recorded alcohol consumption

Reported frequency of consumption	Number of diary days on which alcohol consumption recorded
Almost every day	4
Five or six days per week	4
Three or four days per week	3 or 4
Once or twice per week	1 or 2

For participants who reported drinking 'almost every day', the mean alcohol beverage calories from the four drinking days recorded in their diary were multiplied by 6.5 to give an estimate of their weekly calories from alcoholic beverages. For those who reported drinking 'five or six days per week', the mean was multiplied by 5.5. For those who reported drinking between one and four days per week, no extrapolation was necessary.

4.3.4 Statistical analysis

Appropriate survey data techniques to account for sampling weights, clustering and stratification of the sampled data (using the survey data analysis tools in STATA version 14.2) were used in analyses where possible. Survey weightings, provided in the NDNS datasets, were re-calibrated for use with combined datasets for years one to nine. Survey weightings were used to take account of survey design and non-response. Using these weights and survey data techniques in the analysis ensures that the results are representative of the whole population of the UK living in private households.

Alcohol consumption was categorised by the four different methods described above. Statistical analyses were performed for the different categorisations in turn.

Descriptive statistics were used to describe associations between BMI groups, sociodemographic variables, frequency of alcohol consumption and binge drinking. Appropriate statistical tests were

used to check for independence within groups and these are detailed in the relevant results tables. Descriptive statistics were also used to describe associations between BMI groups, sociodemographic variables and food or alcohol calories. Alcohol calories were not normally distributed, so median values and non-parametric tests were used to describe their distribution. Median values are presented with 95% confidence intervals, rather than Interquartile Ranges, as they are survey estimates. Food and total calories were normally distributed. Mean values and standard statistical tests were used to describe their distribution.

Logistic regression models were used to explore the relationship between obesity and overweight/obesity (as binary dependent variables) with frequency of alcohol consumption and binge drinking. The multivariate models were adjusted for age, sex, employment, education, smoking, diary start day and physical activity. Odds ratios are presented with 95% confidence intervals and statistical significance at two levels (0.05 and 0.01) is indicated.

Alcohol beverage calories, food calories and total calories were compared by diary day and in those who did, or did not, drink alcohol during their diary. For individuals who drank on some, but not all diary days, t-tests were used to compare mean total calorie consumption on the days they did or did not drink alcohol. Alcohol beverages calories were not normally distributed. Median differences in calories from alcohol were explored by BMI, employment and gender using Kruskal-Wallis equality-of-populations rank test, in those who drank alcohol during their diary.

Weekly alcohol consumption was estimated in the subgroup analysis. Descriptive statistics were used to describe associations with sociodemographic factors, and alcohol consumption frequency in the subgroup participants. Total weekly alcohol beverages calories were calculated and explored by BMI, alcohol consumption frequency, binge drinking and sociodemographic variables.

Data were analysed using STATA version 14.2.

4.3.5 Sensitivity analysis

A sensitivity analysis was performed, with regular drinking re-defined as three or four times per week or more often (instead of once or twice per week or more often). This did not have a significant impact on the results.

4.3.6 Misreporting

Misreporting in self-reported dietary methods is a well-documented issue. In order to validate estimates of energy intake from the self-reported dietary records of food and drinks consumed, the NDNS RP included a doubly labelled water (DLW) sub-study of participants in years one and three. The results of the DLW subsample analysis indicated that reported energy intake is 21% below total energy expenditure in males and 23% lower in females, aged 16-64 years. In our sample, DLW data were available for 192 participants. In these participants, reported energy intake was 22% below total energy expenditure in males and 23% lower in females, aged 18-64 years.

4.4 Results

4.4.1 Descriptive statistics

The sample for analysis contained 6,597 adults aged 18 years or older. Descriptive statistics for the sample, by BMI category, are shown in Table 27. 37.8% of the sample were overweight and 26.3% were obese. The proportion of participants in each BMI category varied significantly with age, sex, education, employment, smoking and frequency of alcohol consumption over the last year.

There were no significant baseline differences between those who did, or did not, complete a diary on any particular day of the week. The proportion of participants in each BMI category, who did or did not complete a four day food and beverage diary, did not differ significantly (p=0.1819).

Diary start days varied, but overall the spread of represented days was even. Wednesday was the least represented day amongst the survey participants (n=3479) and Sunday was the most represented day (n=3994).

Among men, overweight was most common (44.6%), followed by normal weight (30.6%) and obese (24.8%). Among women healthy weight was the most common (40.9%), followed by overweight (31.3%) and obese (27.8%).

Table 27: Baseline characteristics of sample, by BMI category

		Healthy weight (BMI 18.5 to <25)	Overweight (BMI 25 to <30)	Obese (BMI≥30)	
Variable categories		% of BMI category within variable categories – weighted proportion			p value
Whole sample (n=6.086)		35.8%	37.8%	26.3%	P<0.001**[d]
Age in years (n=6086)	mean (SE)	42.1 (0.51)	49.4 (0.51)	50.5(0.55)	P<0.001**[c]
	18-24	19.0%	8.1%	6.6%	P<0.001**[a]
	25-49	49.2%	44.7%	39.8%	
	50-64	17.3%	24.6%	31.8%	
	65+	14.6%	22.6%	21.8%	
Sex (n=6086)	Male	41.9%	57.8%	46.1%	P<0.001**[a]
	Female	58.1%	42.2%	53.9%	
Ethnicity (n=6080)	White	88.5%	89.1%	88.7%	P=0.082[a]
	Mixed ethnicity	1.9%	0.9%	1.2%	
	Black	2.4%	2.2%	3.8%	
	Asian	5.1%	6.2%	5.1%	
	Other	2.2%	1.6%	1.2%	
Education (n=5747)	Finished at 16yrs or under	35.2%	47.0%	52.7%	P<0.001**[a]
	Finished at 17 or 18yrs	25.0%	21.5%	22.7%	
	Finished at 19yrs or over	39.8%	31.6%	24.7%	
Employment NS-SEC three class categorisation ł (n=5146)	NS-SEC class 1	55.2%	54.0%	45.5%	P<0.001**[a]
	NS-SEC class 2	10.6%	10.5%	10.3%	
	NS-SEC class 3	34.3%	35.5%	44.2%	
Cigarette smoking status (n=6078)	Current smoker	24.0%	17.7%	17.8%	P<0.001**[a]
	Ex regular smoker	17.1%	25.8%	28.2%	
	Never regular smoker	58.9%	56.5%	54.0%	
Time spent at moderate or vigorous physical activity median (95%CI) (n=3427)		0.73 (0.66, 0.82)	0.79 (0.70, 0.87)	0.49 (0.42, 0.52)	P<0.001**[b]

ł National Statistics Socioeconomic Classification class 1 = higher managerial, administrative and professional occupations, class 2 = intermediate occupations, class 3 = routine and manual occupations[133]

a chi square test b Kruskal-Wallis test c Anova d chi square goodness of fit test

* denotes significance at the 0.05 level ** denotes significance at the 0.01 level

4.4.2 Frequency of reported alcohol consumption over past 12 months and binge drinking

The frequency of reported alcohol consumption (over last 12 months) differed significantly across BMI categories ($p<0.001$) (Table 28). 11% of obese participants and 16% of overweight participants, reported drinking above recommended limits (estimated by reporting drinking at least five days per week). Obese participants were more likely to report drinking never / not in the last 12 months, compared to normal and overweight participants.

Of those drinking at least five days per week (approximation to above recommended UK limits), 32% were normal weight, 46% were overweight and 22% were obese.

The proportion of participants who reported binge drinking did not differ significantly across BMI categories. Of obese participants, 29% reported binge drinking and of overweight participants, 30% reported binge drinking.

Table 28: Frequency of reported alcohol consumption over last 12 months and binge drinking, among the NDNS adult participants, by BMI category

		Healthy weight (BMI 18.5 to <25)	Overweight (BMI 25 to <30)	Obese (BMI≥30)	
		% of BMI category within variable categories – weighted proportion			Chi squared p value
Frequency drank alcohol in last 12 months (n=6079)	Almost every day	8.1%	11.4%	7.9%	P<0.001**
	Five or six days per week	3.9%	5.0%	3.1%	
	Three or four days per week	14.6%	14.5%	11.8%	
	Once or twice per week	34.1%	32.0%	28.1%	
	Once or twice per month	16.2%	14.7%	16.8%	
	Once every couple of months	8.1%	7.4%	11.1%	
	Once or twice per year	6.5%	7.0%	11.8%	
	Not at all	8.4%	7.9%	9.5%	
Binge drinking‡ (n=3958)	Binge drinker	30.4%	30.0%	28.9%	P=0.8123
	Not binge drinker	69.6%	70.0%	71.1%	
Frequency drank alcohol in last 12 months Re-grouped to reflect drinking guidelines (n=6079)	At least five days per week (approximation to above recommended UK limits)	12.0%	16.4%	11.0%	P<0.001**
	Once to four times per week (approximation to within recommended UK limits)	48.7%	46.5%	39.9%	
	Once per month to once per year (infrequent)	30.9%	29.1%	39.6%	
	Not at all	8.4%	7.9%	9.5%	

* denotes significance at the 0.05 level ** denotes significance at the 0.01 level

‡ defined as yes if participants reported drinking >6 units per day for women, >8 units per day for men, on heaviest drinking day

The proportion of binge drinkers varied significantly by age, sex, ethnicity and smoking status (Appendix C.5 Table 39). The proportion of participants who reported differing frequencies of alcohol consumption varied significantly by age, sex, ethnicity, education, employment and smoking (Appendix C.5 Table 40).

4.4.2.1 Food and alcohol calories consumed during the diary

Mean food calories consumed during the diary varied significantly by BMI category (Table 29). In the whole sample, mean food calories consumed during the diary were significantly lower with increasing BMI. Mean food calories were significantly lower with increasing BMI among binge drinkers, non-binge drinkers and those drinking within recommended UK limits. Mean food calories did not vary significantly between BMI groups for those drinking above recommended UK limits of alcohol, infrequently or not at all.

Mean food calories were significantly higher amongst binge drinkers, compared to non-binge drinkers (1767 vs 1696, p<0.001). Mean food calories were significantly lower amongst those drinking above recommend limits of alcohol, compared to those drinking within recommended limits (1687 vs 1742, p=0.009).

Table 29: Mean food calories from the diary, by BMI category and reported frequency of alcohol consumption

		Mean food calories in the food and beverage diary (SD)			
		Healthy weight (BMI 18.5 to <25)	**Overweight (BMI 25 to <30)**	**Obese (BMI≥30)**	**Anova**
Whole sample (n=5980)		1739 (525)	1702 (519)	1644 (494)	P<0.001**
Binge drinking‡ (n=4135)	Binge drinker	1849 (570)	1737 (532)	1724 (515)	P=0.001**
	Not binge drinker	1722 (486)	1720 (495)	1640 (471)	P=0.001**
Frequency drank alcohol in last 12 months Re-grouped to reflect drinking guidelines (n=6731)	At least five days per week (approximation to above recommended UK limits)	1687 (541)	1699 (504)	1711 (448)	P=0.898
	Once to four times per week (approximation to within recommended UK limits)	1799 (518)	1742 (507)	1677 (498)	P<0.001**
	Once per month to once per year (infrequent)	1695 (530)	1672 (536)	1613 (498)	P=0.011
	Not at all	1634 (480)	1597 (523)	1567 (484)	P=0.507
* denotes significance at the 0.05 level and ** denotes significance at the 0.01 level					

4.4.2.2 Logistic regression model – frequency of alcohol consumption over past 12 months and binge drinking

In the unadjusted logistic regression model the odds of being obese was significantly higher in those drinking alcohol infrequently or not at all, compared to those drinking within UK recommended limits. In the multivariate adjusted model, the odds of being obese were significantly greater in those drinking alcohol infrequently compared to those drinking within UK recommended limits (OR1.59, 95%CI 1.24, 2.05) (Table 30). In the multivariate adjusted model, those drinking above recommended limits were significantly less likely to be obese than those drinking within recommended limits (OR 0.67, 95%CI 0.47 to 0.96).

In the adjusted logistic regression model the odds of being obese were not significantly associated with binge drinking (Table 30).

Table 30: Logistic regression analysis showing odds of being obese, by reported alcohol consumption frequency, and by binge drinking. Model adjusted for age, sex, education, employment, smoking and physical activity.

		Odds of being obese (BMI≥30)			
		Weighted n	**Univariate OR (95%CI)**	**Age and sex adjusted OR (95%CI)**	**Multivariate‡ OR (95%CI)**
Frequency drank alcohol in last 12 months (%) Re-grouped to reflect drinking guidelines (n=6079)	Once to four times per week (approximation to within recommended UK limits)	4472	Ref	Ref	Ref
	At least five days per week (approximation to above recommended UK limits)	1354	0.92 (0.72, 1.17)	0.76 (0.59, 0.98)*	0.67 (0.47, 0.96)*
	Once per month to once per year (infrequent)	3249	1.58 (1.34, 1.86)**	1.57 (1.33, 1.85)**	1.59 (1.24, 2.05)**
	Never/not in last year	934	1.39 (1.04, 1.87)*	1.34 (1.01, 1.80)*	1.42 (0.90, 2.24)
Units drunk on heaviest day in last 7 (n=3958)	Not binge drinker	4597	Ref	Ref	Ref
	Binge drinker (≥6 units on heaviest drinking day for women, ≥8 units on heaviest drinking day for men) Not binge drinker	1936	0.94 (0.77, 1.15)	1.09 (0.88, 1.36)	1.05 (0.76, 1.47)

‡ Multivariate model was adjusted for age, sex, ethnicity, education, employment, smoking and physical activity

* denotes significance at the 0.05 level ** denotes significance at the 0.01 level

In the unadjusted logistic regression model the odds of being overweight or obese was significantly higher in those drinking alcohol infrequently or above recommended limits, compared to those drinking within UK recommended limits. In the multivariate adjusted model, the odds of being overweight or obese was significantly greater in those drinking alcohol infrequently compared to those drinking within UK recommended limits (OR 1.41, 95%CI 1.09 to 1.82) (Table 31).

In the logistic regression model the odds of being overweight or obese was not significantly associated with binge drinking (Table 31).

Table 31: Logistic regression analysis showing odds of being overweight or obese, by reported alcohol consumption frequency, and by binge drinking.

		Odds of being overweight or obese (BMI≥25)			
		Weighted n	**Univariate OR (95%CI)**	**Age and sex adjusted OR (95%CI)**	**Multivariate‡ OR (95%CI)**
Frequency drank alcohol in last 12 months (%) Re-grouped to reflect drinking guidelines (n=6079)	Once to four times per week (approximation to within recommended UK limits)	4472	Ref	Ref	Ref
	At least five days per week (approximation to above recommended UK limits)	1354	1.31 (1.06, 1.62)*	0.92 (0.74, 1.15)	0.84 (0.61, 1.16)
	Once per month to once per year (infrequent)	3249	1.20 (1.03, 1.41)*	1.32 (1.12, 1.56)**	1.41 (1.09, 1.82)**
	Never/not in last year	934	1.14 (0.89, 1.47)	1.19 (0.92, 1.54)	1.12 (0.72, 1.74)
Units drunk on heaviest day in last 7 (n=3958)	Not binge drinker	4597	Ref	Ref	Ref
	Binge drinker (≥6 units on heaviest drinking day for women, ≥8 units on heaviest drinking day for men) Not binge drinker	1936	0.96 (0.80, 1.16)	1.16 (0.96, 1.41)	1.21 (0.92, 1.59)

‡ Multivariate model was adjusted for age, sex, ethnicity, education, employment, smoking and physical activity

* denotes significance at the 0.05 level ** denotes significance at the 0.01 level

4.4.3 Alcohol consumed during four day diary

The 53% of participants (n=3,468) who drank alcohol during the four days of the diary were significantly older, more likely to be male, more likely to be of white ethnicity, more likely to have stayed in education for longer, more likely to be professionals, more likely to be an ex-smoker, more likely to be more physically active and had lower BMI than those who did not drink during the diary ($p<0.001$ for all).

Mean total calorie consumption recorded in the diary, for all participants combined, was highest on Saturday both for those who drank alcohol (mean 2283 kcal) and for those who did not drink alcohol (mean 1688 kcal) (Figure 25). Total food calories were significantly higher in those who consumed any alcohol during their diary, compared to those who did not (mean 1807 vs 1648, $p<0.001$).

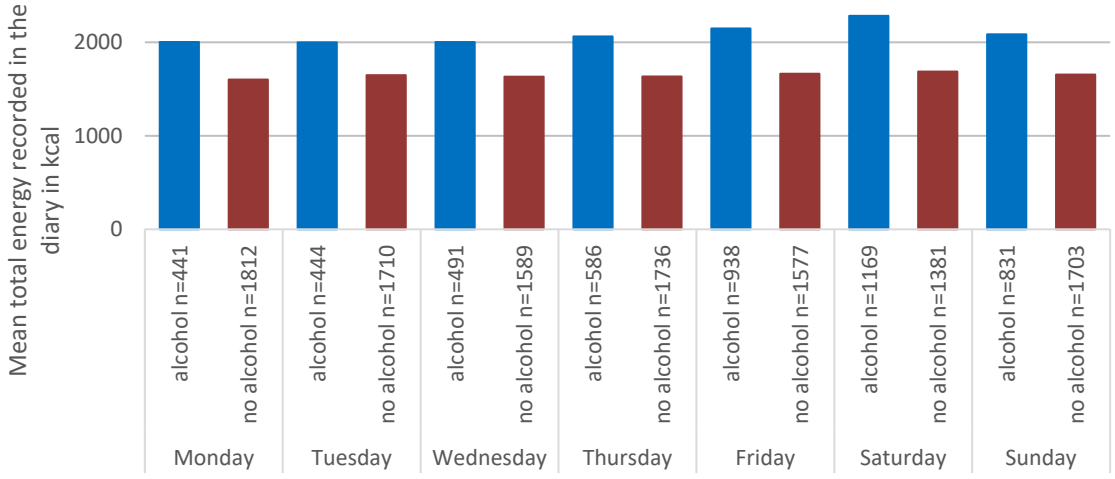


Figure 26 Mean total calories consumed, by diary day, for participants who did or did not consume alcohol on that day. All four day diary completers are included.

The proportion of total calories from alcoholic beverages varied according to day of the week, with Friday (20.2%) and Saturday (21.5%) having the greatest proportion of calories from alcohol beverages (in those who drank alcohol on that diary day) (Table 32).

Table 32: Total calories from food and alcohol in the four day diary, by day of the week and by those who did or did not consume alcohol on that day.

Day of week	N	Alcohol consumed on diary day?	Total kcal consumed on diary day	Total food kcal consumed on diary day	Total alcohol beverage kcal consumed on diary day	Proportion of total calories from alcoholic beverages
Monday	3629	Alcohol	1401194	1183477	217717	15.5%
		No alcohol	4720331	4720331	0	0
Tuesday	3520	Alcohol	1433438	1210335	223102	15.6%
		No alcohol	4595741	4595741	0	0
Wednesday	3479	Alcohol	1617657	1349537	268120	16.6%
		No alcohol	4378506	4378506	0	0
Thursday	3710	Alcohol	1840720	1526489	314231	17.1%
		No alcohol	4551236	4551236	0	0
Friday	3975	Alcohol	3078161	2456387	621775	20.2%
		No alcohol	4185625	4185625	0	0
Saturday	3941	Alcohol	3903425	3064899	838527	21.5%
		No alcohol	3764874	3764874	0	0
Sunday	3994	Alcohol	2651282	2205319	445963	16.8%
		No alcohol	4467406	4467406	0	0

Calories from mixers contributed between 1.6% (Sunday) and 3.6% (Saturday) of total alcohol beverage calories. Alcoholic beverages contributed a median 556 kcal (95%CI 532 to 570) in total, to the calorie consumption of those completing a four day diary and consuming any alcohol during those four days. Alcoholic beverages contributed a median 190 – 334 calories per day to participants' total calorie intake, depending on day of the week. Alcohol beverage calories contributed the most on a Saturday (median 334 kcal, 95%CI 315 to 352) and least on a Monday (median 190 kcal, 95% 187 to 210).

Median calorie consumption from alcoholic beverages for the whole diary, for those who drank alcohol during four days of the diary, was significantly higher in men (760 kcal, 95%CI 725 – 822), compared to women (416 kcal, 95%CI 394 – 444) p<0.001. Median calorie consumption from alcoholic beverages also varied significantly by BMI category (p<0.001) and by employment (p=0.04) (Figure 27, Figure 28).

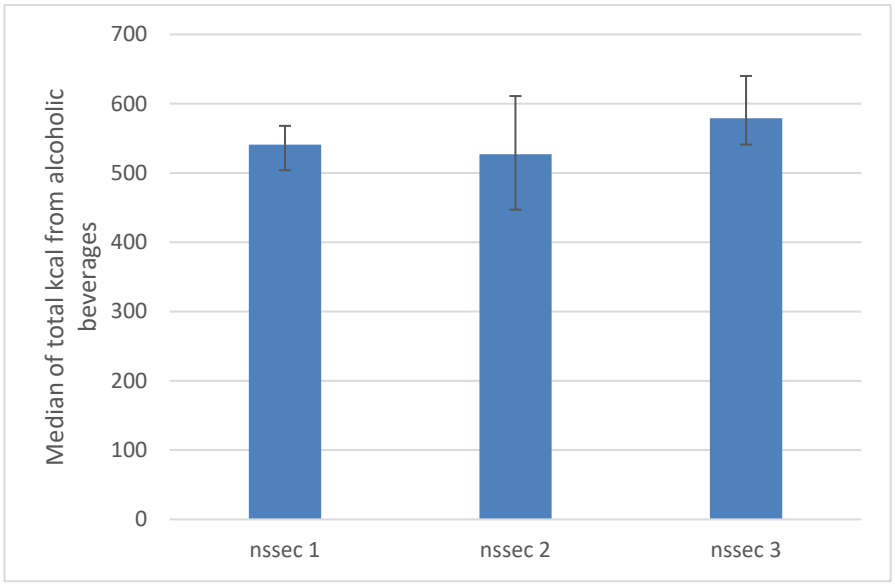


Figure 27: Median total calories from alcohol beverages in the four day diary, by employment. Includes only those who completed a four day diary and consumed some alcohol during their diary days. Error bars indicate 95% confidence intervals.

nssec 1 = higher managerial, administrative and professional occupations
nssec 2 = intermediate occupations
nssec 3 = routine and manual occupations

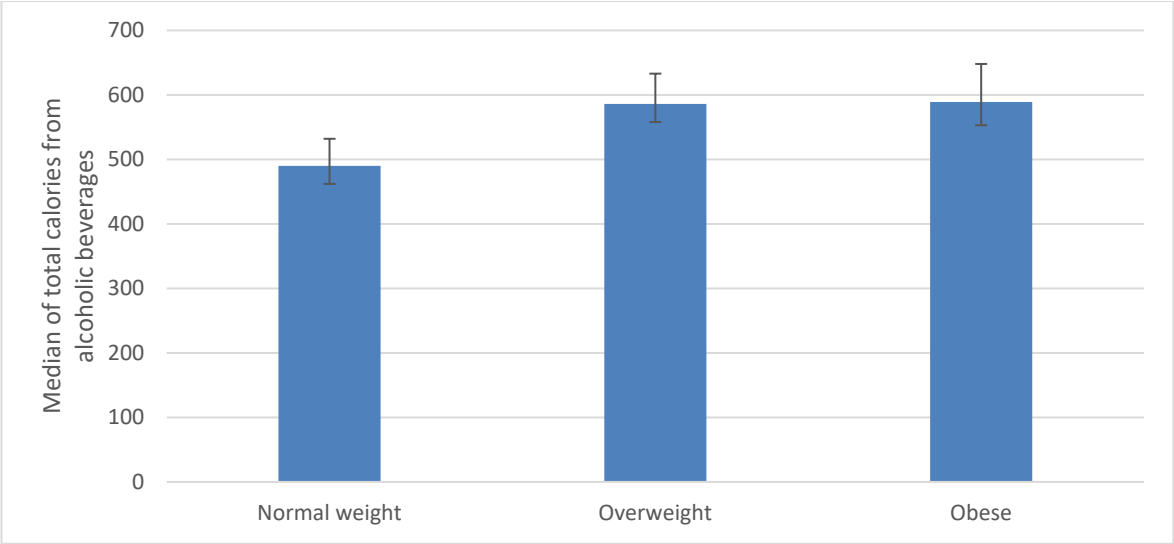


Figure 28: Median total calories from alcoholic beverages in the four day diary, by BMI category, Includes only those who completed a four day diary and consumed some alcohol during their diary days. Error bars indicate 95% confidence intervals.

4.4.4 Subgroup with accurate estimate of weekly alcohol consumption

Participants entered the subgroup (n=1925) if the alcohol consumption recorded in their diary, matched the alcohol consumption reported in their interview, and could therefore be considered a true reflection of their weekly consumption (see methods). All subgroup participants consumed some alcohol during their four-day diary.

Participants in the subgroup were significantly older, more likely to be male, more likely to be of white ethnicity, more likely to be professionals, more likely to be an ex-smoker, more likely to be more physically active and had lower BMI than the whole sample. Participants did not differ significantly by education status.

Subgroup participants who reported drinking only once or twice per week, were most likely to do so on a Friday, Saturday or Sunday (Figure 28).

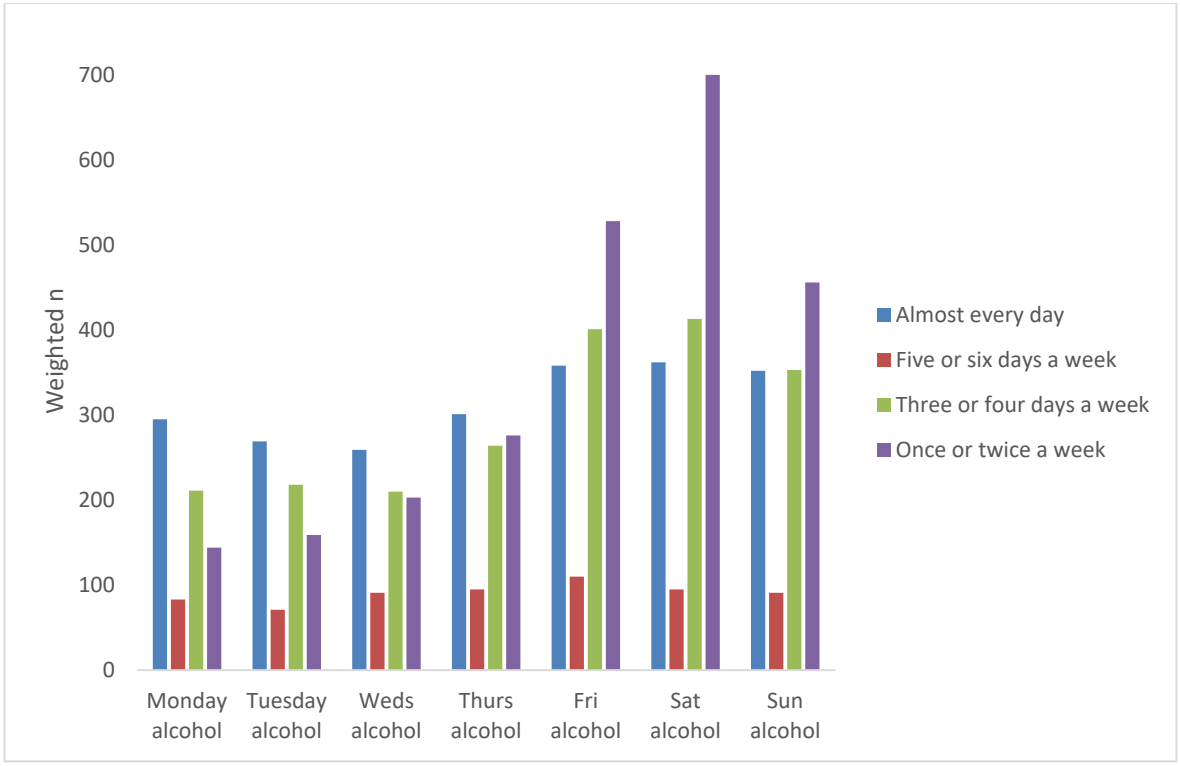


Figure 29: Graph showing days on which participants consumed alcohol, by frequency of alcohol consumption, for subgroup participants whose diary alcohol consumption matched their questionnaire responses

Estimate of weekly calorie contribution from alcoholic beverages

Total weekly alcohol beverage calories were calculated in the subgroup, extrapolating from the information in the four-day diary, to estimate weekly calories due to alcoholic beverage consumption (see methods). This includes calories from alcohol, and soft drinks consumed with alcohol such as mixers.

Total weekly alcohol beverage calories were significantly higher in binge drinkers (median 1123 kcal binge vs 552 kcal non-binge, $p<0.001$). Binge drinkers consumed an extra median 571 calories per week from alcoholic beverages

Total weekly alcohol beverage calories were significantly higher in participants drinking above recommended limits of alcohol, compared to those drinking within limits (median 2079 vs 504, $p<0.001$). Participants drinking above recommended limits of alcohol consumed an extra median 1575 calories per week from alcoholic beverages.

For the subgroup as a whole, median weekly alcohol beverage calories increased significantly with increasing BMI (Table 33). Median weekly alcohol beverage calories increased significantly, with increasing BMI, for those drinking alcohol within recommended limits. Median calories from alcohol did not vary significantly across BMI groups for binge drinkers and those drinking alcohol above recommended limits (Table 33).

Table 33: Median weekly calories from alcoholic beverages in subgroup, by BMI category, frequency of alcohol consumption and binge drinking. Subgroup participants were alcohol consumers who completed a four day diary and whose alcohol consumption in the diary, matched their self-reported alcohol consumption in the questionnaire.

		Median weekly calories from alcoholic beverages in subgroup, within BMI category Median kcal (95% CIs)			
		Healthy weight (BMI 18.5 to <25) n=647	**Overweight (BMI 25 to <30) n=725**	**Obese (BMI≥30) n=449**	**Kruskall Wallis test**
Whole subgroup (n=1925)		560 (514, 646)	687 (632, 763)	775 (688, 924)	P<0.001**
Units drunk on heaviest day in last 7 (n=1810)	Binge drinker	991 (855, 1141)	1108 (936, 1315)	1324 (1161, 1532)	P=0.051
	Not binge drinker	461.8 (402, 517)	619 (552, 667)	584 (514, 687)	P=0.002**
Frequency drank alcohol in last 12 months Re-grouped to reflect drinking guidelines (n=1925)	At least five days per week (approximation to above recommended UK limits)	1856 (1627, 2247)	2297 (1809, 2878)	2246 (1969, 2600)	P=0.184
	Once to four times per week (approximation to within recommended UK limits)	437 (397, 489)	529 (470, 569)	570 (514, 647)	P<0.001**
* denotes significance at the 0.05 level and ** denotes significance at the 0.01 level					

At the subgroup population level, mean total calories per day in the diary were significantly higher for days on which participants drank alcohol, compared to days on which they did not (mean 2141 kcal vs mean 1713 kcal, p<0.001). Subgroup participants consumed an extra mean 428 kcal per day on days they drank alcohol, compared to days they did not (mean difference 428 kcal (95%CI 396 – 460, p<0.001). Subgroup participants consumed a small but statistically significant extra mean 36 calories from food on days they drank alcohol, compared to days they did not (mean 1748 kcal vs mean 1713 kcal, p=0.012).

Median weekly calories from alcoholic beverages varied significantly by age, sex, educational attainment and cigarette smoking (Table 34). Median weekly calories from alcohol beverages were significantly higher in males – more than twice the median seen in females. Median weekly calories from alcoholic beverages were highest in those who left education earliest and in current smokers.

Table 34: Median weekly calories from alcoholic beverages, by sociodemographic factors

		Median weekly calories from alcoholic beverages (95% CIs)	**Kruskall Wallis test**
Age (n=1925)	18-24 25-49 50-64 65+	686 (498, 870) 652 (587, 686) 750 (652, 918) 662 (599, 758)	P=0.046*
Sex (n=1925)	Male Female	1019 (936, 1103) 481 (430, 525)	P<0.001**
Ethnicity (n=1925)	White Mixed ethnicity Black Asian Other	676 (647, 726) 460 (248, 1280) 444 (253, 1005) 334 (249, 743) 609 (233, 892)	P=0.062
Education (n=1860)	Finished at 16yrs or under Finished at 17 or 18yrs Finished at 19yrs or over	750 (680, 855) 564 (516, 665) 635 (570, 709)	P<0.001**
Employment NS-SEC three class categorisation ł (n=1666)	NS-SEC class 1 NS-SEC class 2 NS-SEC class 3	653 (598, 706) 673 (524, 820) 680 (627, 753)	P=0.187
Cigarette smoking status (n=1925)	Current smoker Ex regular smoker Never regular smoker	1053 (891, 1177) 747 (669, 872) 533 (492, 569)	P<0.001**

ł National Statistics Socioeconomic Classification class 1 = higher managerial, administrative and professional occupations, class 2 = intermediate occupations, class 3 = routine and manual occupations[133]

* denotes significance at the 0.05 level ** denotes significance at the 0.01 level

4.5 Discussion

4.5.1 Summary of main findings

In this analysis of data collected in the NDNS RP, associations between alcohol and obesity were non-linear and complex, as concluded in recent reviews.[120-122 124] More people consumed alcohol than did not, across all categories of BMI, suggesting that alcohol calories contribute to daily calorie intake in the majority of the population. Alcohol consumption varied significantly by diary start day, with maximum consumption on Friday and Saturday and those drinking only once or twice per week were most likely to do so on Friday or Saturday.

On any given day of the week, calorie consumption was higher in those who consumed alcohol than those who did not and alcohol calories were consumed in addition to, not instead of, other calories. For those who drank alcohol on some, but not all diary days, their total calorie consumption was significantly greater on the days on which they drank alcohol (mean difference 428 kcal (95%CI 396 – 460, $p<0.001$). This is the equivalent of consuming an extra 1.4 hamburgers per day.[136]

Weekly calories from alcoholic beverages were calculated in a subgroup for whom this could be estimated. Weekly calories from alcoholic beverages were more than twice as high in males as females, and twice as high in current smokers compared to never smokers. Weekly calories from alcoholic beverages, measured in the diary, increased significantly with increasing BMI. This is in contrast to mean food calories measured in the diary, which decreased significantly with increasing BMI. Under-reporting of food calories with increasing BMI is an acknowledged phenomenon in the NDNS and other dietary surveys.[137-139] This finding suggest that under-reporting of alcohol calories does not occur in the same way. It also suggests that alcohol calories make a significant contribution to total calorie intake in overweight and obese people who consume alcohol at least once per week. It must be remembered that the majority of obese participants reported never drinking alcohol.

4.5.2 Methodological issues

The NDNS food diary data was collected over three or four days. Our analysis has clearly shown the significant variation in quantities of alcohol consumed, by day of the week. This variation

makes it difficult to predict weekly alcohol consumption, based on a three or four day snapshot, which may or may not have included a weekend. Diaries not including a weekend would underestimate weekly consumption and diaries including a weekend would overestimate weekly consumption. Any weighting by day of the week could not be applied to those who did not consume any alcohol during their food diary (n= 1856) but who may habitually consume alcohol. Misclassification bias would be very high.

The inability to accurately assess weekly alcohol consumption from the data has limited the conclusions that can be drawn from it. We would strongly recommend that future research attempts to collect alcohol data for at least one week in duration.

4.5.3 Strengths

The NDNS RP is a robust, high quality dietary survey. We have used detailed information about alcohol consumption, where other studies have only used information about the heaviest drinking day. We have been able to consider alcohol calories as a proportion of total calorie intake. This is a particular strength of the study, as previous work using the Health Survey for England has only been able to measure against UK recommended daily calorie allowance (RDA)[123]. Previous studies have calculated the calories in an alcoholic drink using the grams of ethanol it contains. We have used precise information on calories associated with alcohol type, reflecting the difference in calories between drinking ten grams of ethanol in wine and ten grams of ethanol in beer. We have also created a variable for 'alcoholic beverage' that included any soft drink mixers consumed at the same time as alcohol. This avoids the frequently encountered problem of under-estimation of calories from spirits. We believe our assessment of calories from alcohol is therefore much more robust than has been previously achieved.

Other strengths of this study are that BMI data were from physical measurements taken by a nurse, rather than self-report and that we were able to adjust for many of the variables which are thought to influence the relationship between alcohol and obesity (age, sex, employment, education, smoking and physical activity). This has not been possible in other epidemiological studies[120 122]. However, in such a complex relationship there are likely to be other contributing factors that we have not adjusted for and the likelihood of residual confounding is still high.[122 125]

Our sensitivity analysis and subgroup analysis findings were similar to those of the main analysis, which increases confidence that the methods used to stratify alcohol consumption were appropriate.

4.5.4 Limitations

Many people's drinking habits change, both over the short and long term, and some people do not report alcohol consumption accurately. Misreporting of calorie consumption is an acknowledged methodological flaw in the NDNS and other self-reported diary surveys[138 139]. Misreporting in our sub-sample (n=192 for whom DLW data was available) was very similar to that demonstrated in the NDNS RP overall, with under-reporting more common in women than in men.[137] Other work has shown the degree of misreporting to correlate with increasing BMI[138 139] and in our sub-sample, under-reporting of calories was greatest in obese participants across all gender and age categories. Misreporting may also vary by alcohol consumption group. Under-reporting of alcohol consumption is a common phenomenon. Zhang et al.[140] found over-reporting of total and non-alcoholic energy intake in those who consume alcohol, with greatest over-reporting in male heavy drinkers. If this type of misreporting occurred in the NDNS RP data, it would result in an underestimation of the extra calories from alcohol, as a proportion of total calorie intake. We would therefore expect the additional calories from alcohol to be even greater than demonstrated here. We have no reason to suspect that the extent of misreporting would vary for individuals between days they did and did not consume alcohol, so this should not have influenced our finding of greater calorie intake on days that individuals consumed alcohol, compared to days they did not.

Drinking patterns and trends vary considerably from country to country, in terms of both the type of alcoholic beverages consumed (and their calorie content) and the way in which they are consumed in relation to food. For example, in 2016, 49% of alcohol consumed in France was wine[141]. In the UK, this figure was only 18%[141]. The total volume of alcohol consumed per capita ranged from 75.4 litres in France, to 113.8 litres in the UK and 142.3 litres in Germany[141]. These societal variations in how different countries consume alcohol are likely to influence the associations seen between alcohol and weight gain. The results of this study may not therefore be generalisable outside the UK population.

4.5.5 Other studies

Previous analysis of NDNS data from year one found that for adult consumers of alcohol, alcohol contributed nearly 10% of calories[142]. Our analysis showed that over years one to six, in adult consumers of alcohol, alcohol calories contributed 17.9% of total calorie intake suggesting a significant increase in alcohol consumption since the survey began. The National Health and Nutrition Examination Survey 2007-2010, in the USA, showed similar levels with adult consumers

of alcohol obtaining approximately 16% of their total energy intake from alcoholic beverages.[143] Other studies have confirmed our finding that alcohol drinking is more common at the weekend in the UK (and in Europe.)[144]

There is a need for accurate alcohol consumption data of at least one-week's duration to be collected, which is ideally independently validated rather than self-reported.[124] Such data would allow alcohol consumption to be classified more accurately, with reference to current recommended guidelines. Comparisons could then be made between those drinking above or below guideline amounts. This would inform future revision of guidelines and would help to keep public health messages clear and consistent. Diary data are extremely useful for detailed analysis of consumption patterns, however even one week of diary data may not be an accurate representation of a person's 'average' consumption.

4.5.6 Implications

Calories from alcohol are 'empty' calories, with no nutritional value. Many overweight and obese people do not consume alcohol. However, the findings of this analysis suggest that there are strong associations between alcohol calories and overweight/obesity in those who consume alcohol regularly. People who are both overweight/obese and consume alcohol above the recommended UK limits are at increased risk of liver disease from two mechanisms: direct damage to the liver from alcohol and indirect damage from the contribution of alcohol calories to increased BMI. Reducing calories from alcohol could provide a valuable intervention to reduce risk in this group. Most lower alcohol alternatives, such as low alcohol lager, also contain fewer calories. Under the Public Health Responsibility Deal, the drinks industry undertook a voluntary pledge to provide information on alcohol calories to consumers but in a recent review of UK supermarkets, only 1.3% of alcohol products showed calorie information on their labels.[145] Many people do not know how many calories are in alcoholic beverages.[120] Clear labelling of the calorie content of alcoholic beverages, as recently called for by the Royal Society of Public Health[146], could raise awareness and help people to make healthier, more informed choices.

Friday and Saturday were the days of highest calorie intake from alcohol. They were also the days on which people who only drink once or twice per week, were most likely to drink. This is important when considering public health interventions aimed at reducing alcohol consumption. Reducing consumption of alcoholic beverages, especially at weekends, would reduce overall calorie consumption.

Obesity is predicted to be a greater problem in men than in women in the future[118]. Men consume more alcohol than women, and the calories from alcoholic beverages for men in this NDNS analysis were far greater than for women. Targeting alcohol calories could be an effective strategy for public health messages aimed at obesity in men. Reducing alcohol consumption would also reduce risk of liver disease and alcohol related harms. The suggestion of tailored alcohol consumption guidance, with lower limits for those who are obese or have type 2 diabetes has been made here, in order to reduce risk of liver disease from a combination of harms. Tailored guidance would also limit the calories from alcohol that these people may consume, with potential benefits for their weight management and metabolic health.

Targeting messages about alcohol reduction in those who are already obese may help as part of weight reduction strategies. However, 21% of obese participants in the NDNS drank alcohol only once or twice per year, or not at all. Rose[44] showed that a small reduction across everyone is more significant for the health of a population, than tackling a small subgroup such as the morbidly obese. In the UK, where obesity and alcohol consumption are both increasing more than the rest of Europe, our focus should perhaps be on changing the norm.

Chapter 5: Discussion

5.1 Overview

This thesis has focused on liver disease due to alcohol consumption and overweight/obesity in the UK. The overarching aim was to add to knowledge about how liver disease can be prevented, and detected early, in the general population. The main findings are summarised and discussed here. Strengths and limitations of this work, implications for policy & practice and plans for future work are also discussed in this chapter

5.2 Preventing liver disease

As discussed in chapter one, primary prevention measures aim to prevent or delay the onset of disease. Measures could take place at the whole population level, or be targeted at high risk groups. Results from this thesis support both these approaches, and are summarised here:

5.2.1 Whole population approaches to prevention

This thesis has demonstrated that the vast majority of the general population of the UK have risk factors for liver disease. In England, from HSE data an estimated 89% of the population had at least one risk factor for liver disease. Risk factors were defined as BMI ≥ 25, alcohol consumption above UK recommended limits (>14 units/week), high or very high waist circumference or diabetes. Nearly one quarter of the population were estimated to be drinking above recommended UK limits of alcohol consumption, and 64% were overweight or obese. From nine years of UK data in the NDNS, 64% of the UK population were overweight or obese. Worldwide, from general population cohort studies described in chapter two, the proportion of overweight and obese participants ranged from 33% to 72% and the best estimation of the proportion drinking alcohol above recommended limits ranged from 5% to 38%.

This reflects, as Geoffrey Rose described it, that we are a 'sick population'.[44] Following Rose's principles, a small reduction in risk factors across the whole population could have a great effect on reducing the number of people who get liver disease. For example, data from the Framingham heart study indicated that a 10mmHg reduction in blood pressure across the whole population, would result in a 30% reduction in mortality.[44]. What, then, might be the reduction in liver disease at a population level from a relatively small overall reduction in BMI and alcohol consumption? As

alcohol and obesity are both risk factors for many other chronic diseases, the population health benefit from a small overall reduction would likely be great.

5.2.2 High risk group approaches to prevention

Targeting high risk groups is another strategic approach to prevention. For this to be effective, those at greatest risk must be correctly identified. The risk of liver disease in high risk alcohol consumers is well documented, but agreement on the degree and nature of risk in those with a combination of BMI and alcohol risk factors has been less clear. The meta-analysis presented in chapter two is the first meta-analysis to investigate this combined risk. The results demonstrated that there was no statistical interaction between alcohol consumption and BMI, on risk of liver disease. However, there was a multiplicative risk of liver disease in those with a combination of increased BMI and alcohol consumption. Compared to participants who drank alcohol within the recommended UK limit and who were normal weight, participants who were overweight and drank alcohol above recommended limits were 3.6 times more likely to develop cirrhosis. Participants who were obese and drank alcohol above recommended limits were 5.8 times more likely to develop cirrhosis. A subgroup analysis showed that risk may be highest for those who are obese and consuming high risk quantities of alcohol (defined as >42 units per week in this subgroup analysis). However, this subgroup analysis included only one study, rated of poor quality, so caution is required when interpreting these results. Further evidence on risk associated with higher strata of alcohol consumption, in the presence of overweight/obesity would be valuable. Without clear information about the risk of liver disease associated with particular risk factors, healthcare professionals cannot communicate this risk clearly to patients, or advise them appropriately. Without clear understanding of these risks, patients cannot make informed choices about their health. Our aim was therefore to provide robust estimates of the risk of liver disease associated with combinations of increased BMI and alcohol consumption. These are presented in a simple visual form (Figure 17) for use by patients, healthcare professionals and policy makers. The data presented in figure 17 are relative risks and should be considered alongside the absolute risk of disease. However, concepts such as relative risk (and the difference between absolute and relative risk) may not be easily understood by the general population. Work with Patient and Public Involvement groups, and colleagues who specialise in communicating risk, would be important in designing an infographic to clearly convey information about the risk of liver disease associated with increased alcohol consumption and increased BMI to the general population.

There is currently no formal name for liver disease caused by a combination of obesity and alcohol consumption. We proposed the term ‘BAFLD’ which simply stands for **B**oth **A**lcohol and **F**atty **L**iver **D**isease. The fact that there is no name for this group suggested to us that they are not

recognised as a high risk group, yet the meta-analysis results have shown that they are at significantly increased risk of liver disease . The HSE data estimated the proportion of the population who are at risk of BAFLD, due to intermediate risk alcohol consumption and increased BMI, to be 12%. A further 1.5% are high risk alcohol consumers, who are also overweight or obese, and are likely to be at even greater risk of liver disease. We have not included these people in our definition of BAFLD, as their risk assessment and clinical care are likely to be driven by their alcohol consumption. However, the exact definition should be agreed by clinical experts in the field.

Clustering of risk behaviours is common.[48] Analysis of the HSE sample showed that 28% of the population had multiple risk factors for liver disease. Of participants in the highest risk category for alcohol consumption: 6.6% also had diabetes, 29.8% were obese and 47.0% had a very high waist circumference. The proportion of the sample with multiple risk factors for liver disease increased significantly as educational attainment decreased. However, the relationship with deprivation was not statistically significant. The proportion of the sample with multiple risk factors for liver disease was significantly lower in routine/manual workers. These results demonstrate that relationships between socioeconomic factors and risk factors are complex.

Health inequalities are wide in the UK. Life expectancy for the most deprived in our society is nine years less than for the least deprived, and the difference in the number of years lived in good health between the most and least deprived, is 19 years.[147] The most deprived are more likely to be obese and more likely to suffer poor outcomes from a wide range of diseases, including liver disease and alcohol-related harms.[37] These relationships are complex and there are many unknowns. In the HSE sample, risk factors for NAFLD were significantly more likely in the most deprived, but risk factors for BAFLD were significantly less likely in the most deprived. As more evidence about different groups of patients at risk is identified, prevention strategies can be more effectively targeted.

In summary there are clear populations who are at particularly high risk of liver disease, and who should be targeted by high risk prevention strategies.

5.2.3 Interventions

Both the whole population approach, and the high risk approach to primary prevention are only effective if there are suitable interventions to reduce the risk of disease onset. Interventions may occur at different levels – for example actions at government and societal levels to reduce health inequalities, but individual behaviour changes to modify risk behaviours. Alcohol consumption and overweight/obesity are both risk factors that can potentially be modified by action at multiple

levels. Actions at government level include minimum unit pricing for alcohol, soft drinks levy, ending the sale of energy drinks to children, mandatory calorie labelling, watershed on advertising of foods high in fat, sugar and salt, planning decisions to promote active lifestyles behaviour changes.

An individual's ability to change their behaviour depends on many factors – environmental, societal, personal and behavioural - and this is too large a topic to do justice to here. Understanding the reasons why change is desirable, is a necessary step for action at an individual level. Understanding of the causes of liver disease amongst the general population has been shown to be low.[46 47] This was confirmed by the HSE data showing only 4.4% of the population were aware that they were at risk of liver disease, despite 89% having at least one risk factor and 28% having multiple risk factors for liver disease. Public health messaging about risk factors for cardiovascular disease appears to have been more successful than that for liver disease, with a greater proportion of the population reporting awareness of those risk factors.[106 107] Improvement is therefore possible. The NDNS analysis showed that alcohol calories may play an important part in the diet of those who are overweight and obese. Clearer labelling of the calorie content of alcoholic beverages could help people to make more informed decisions.

The healthcare system offers many opportunities for action to prevent disease. Alcohol and overweight/obesity are risk factors for many chronic diseases, in addition to liver disease. There are many existing health programmes which could be adapted to include discussion of risk factors for liver disease, and brief interventions to facilitate behaviour change. Brief interventions (short discussion including advice or counselling) from healthcare professionals have been shown to be effective in reducing alcohol consumption.[148]

NHS health checks are offered to the population of England aged 40 to 74 years. They take place in primary care or community settings and consist of an interview, physical measurements and blood tests. They are designed to detect diseases early, so that interventions can be made to change risk behaviours and improve outcomes. The health check was designed to detect early signs of stroke, kidney disease, heart disease, type 2 diabetes or dementia.[149] Risk factors relevant to liver disease, such as alcohol consumption and BMI, have always been explored in the health check but were previously not discussed or acted on with respect to liver disease.

The best practice guidance for NHS health checks changed in 2019, so that these risk factors are now also considered in the context of liver disease. For example, if a patient has a high risk alcohol assessment they should be offered a non-invasive test for liver fibrosis in the form of an ELF test or transient elastography (Fibroscan®). Reference to the relevant NICE guidance for liver disease are now included in the alcohol, diabetes, eating healthily and physical activity sections of

the health check.[39] An alcohol brief intervention/advice is delivered to all those drinking above low risk. The potential impact of calories from alcohol is also included, with guidance stating that discussions around energy intake should include alcohol, and the link between alcohol intake and obesity should be highlighted with respect to liver disease.[39] However, assessment for cirrhosis is only triggered by high alcohol consumption (an AUDIT score of 16 or above), not by obesity or a combination of more than low risk alcohol consumption and obesity.

The QRISK® score is a prediction algorithm for cardiovascular disease, which uses a combination of sociodemographic data, clinical data, blood test results and physical measurements to estimate a person's risk of developing cardiovascular disease over the next 10 years.[150] This has been well validated and has been integrated in to the NHS health check cardiovascular assessment.[39 151] Data from existing GP systems, such as EMIS and SystmOne, can be automatically transferred to the QRISK® calculator, which makes the process simpler and less time consuming for GPs. It is already known that many GPs lack confidence in diagnosing and managing liver disease.[89] Development of a similar prediction algorithm for liver disease would be of value in identifying those at highest risk, and in supporting primary care professionals to manage their care.

The new Diabetes Prevention Programme would be another example of an opportunity to identify those at risk, intervene and prevent liver disease within existing healthcare programmes. This programme aims to identify those with risk factors for diabetes, in order to intervene and encourage weight loss and physical activity. The overlap with risk factors for NAFLD in this group is significant. The HSE analysis showed that the highest proportion of participants who were aware they were at risk of liver disease, was among people with diagnosed diabetes. This indicates that discussions about risk factors for liver disease may already be taking place as part of diabetes care, and any opportunities to build on this should be explored.

The NHS long term plan, released in 2019, stated one of its key ambitions as 'preventing illness and tackling health inequalities'. It included a commitment to 'help people make healthier lifestyle choices and treat avoidable illness early on.' Alcohol and obesity were both mentioned as risks to be tackled. Whilst there were no direct commitments for action to prevent liver disease in the plan, the actions to reduce obesity, alcohol consumption and health inequalities will all also help to prevent liver disease.

The UK government have further emphasised their commitment to prevention. 'Prevention is better than cure' published in 2018 set out their vision for 'putting prevention at the heart of our nation's health'[152] and was followed by the prevention green paper in 2019.[153] There was recognition in this document that prevention needs to occur across the life-course; to tackle the root causes of poor health; to target services for high risk people; to address health inequalities

and the wider determinants of health. The government has also pledged to halve childhood obesity by 2030.[154] If this target can be achieved, it will significantly reduce the burden of liver disease due to obesity as the next generation age.

UK guidelines on safe limits for alcohol consumption have been set universally. They do not take any account of co-morbidity, despite 64% of the population being overweight or obese.[39]. The meta-analysis presented here confirms that these people are at significantly increased risk of liver disease; multiplicatively increased if they also consume alcohol above the UK limit. Policy makers could consider the introduction of tailored alcohol guidelines, to better serve the UK's increasingly co-morbid population, and to mitigate the impact of combining alcohol consumption with those co-morbidities.

5.3 Detecting liver disease

The HSE general population sample showed unique features in the distribution of liver blood tests and fibrosis scores. Of the whole sample, 10.9% had an abnormal ALT or AST result. This was approximately half the prevalence of abnormal ALT or AST found in the ALFIE study, which looked at patients who had had liver blood tests taken in primary care.[108] The prevalence of a 'high' result for fibrosis scores varied considerably, from less than one percent to nearly ninety percent, depending on the test/score. This corresponds with research showing the prevalence of liver fibrosis varied from 0.7% to 25.7% in the general population, depending on the non-invasive test used.[54] The AST:ALT ratio was high in 71% of the HSE sample. As a high BARD score was automatically triggered, if the AST:ALT ratio was raised, the BARD score was also high in a large proportion of the population (88%).

Improvements in the early detection of liver disease need to be made, in order for intervention to occur before disease becomes irreversible.[2 32 56] However, the best way to do this still remains unclear. Serum liver enzymes ALT and AST have long been used, and are still used, as markers of liver disease despite the fact that their sensitivity for detecting disease is low. Not only does significant fibrosis occur without raised liver enzymes, but raised liver enzymes occur in a large proportion of patients without liver disease. Two large primary care cohort studies have confirmed this. The BALLETS study found liver disease in less than 5% of patients with raised liver enzymes and the ALFIE study found liver disease developed in only 1.1% of patients with raised liver enzymes (over a relatively short follow up period, median 3.7 years).[155 108] In spite of this, abnormal liver enzymes are often the starting point of many liver disease investigation algorithms.[58]

The AST:ALT ratio has been recommended for the detection of liver disease in general population settings. The BSG guidelines suggest that the AST:ALT ratio may be used to assess significant fibrosis in adults with abnormal liver blood tests. They go on to state that "the utility of the AST:ALT ratio in adults persists even if both values are within the normal reference interval".[58] The results presented here would strongly suggest that this is not the case. The AST:ALT ratio has been shown to have a NPV of 93%[24] in patients with NAFLD (in a selected population at a tertiary referral centre), and it has been recommended by the Lancet Commission to rule out significant fibrosis in NAFLD patients in primary care.[2 110] However, NAFLD patients are not the same as the general population, as the results presented here clearly show. Generalisation of results from NAFLD populations to the general population may result in sub-optimal standards of care.

Most of the tests and scores currently used to detect fibrosis have been developed and validated in secondary care populations with existing liver disease. Their performance characteristics in these groups may differ significantly from those in the general population. New pathways for risk assessment and stratification have been developed in some areas, which aim to better reflect the general population and to help GPs with difficult decision making. The 'scarred liver project' in Nottingham was designed to detect liver disease earlier in the community, with a focus on risk factors as well as abnormal liver blood tests, as the trigger for investigation.[156] The AST:ALT ratio is then used subsequently, to further stratify patients, but only in the presence of abnormal ALT or AST. When compared to an approach using abnormal liver enzymes only to trigger further investigation, this risk factor based approach detected an extra 55 patients with significant liver disease (out of 744 patients).[156]

The concordance of liver blood tests and non-invasive markers of fibrosis in the HSE sample was poor (Table 19). Only 11 out of 85 participants who had a high FIB-4 score, also had a high ALT. This corresponds with previous studies in the general population, which found 40-75% of patients with liver fibrosis had a normal ALT level.[54] Although we did not have any liver disease outcome data for the participants, the lack of overlap in positive results for different tests and markers suggests that sensitivity might be improved by using combinations of tests. Using a combination of the ELF test and the NAFLD fibrosis score, gave better sensitivity and specificity than either test alone (Table 3).[26]

Elsewhere, the Intelligent Liver Function Testing (iLFT) system has been designed to automatically generate further testing in the laboratory, if an abnormal liver blood test result is found.[112 157] The aim of the iLFT system was to increase appropriate investigation, diagnosis and management for patients.[157] FIB-4 and the NAFLD Fibrosis Score are used as fibrosis staging algorithms within the

system. Evaluation of the system showed a 43% improvement in diagnosis of liver disease compared to the control arm receiving usual care (95% CI 27–59%, p <0.0002).[157]

The variation in care for liver disease patients, at both primary and secondary care levels, across the UK has been acknowledged.[2] Decision-making tools for GPs are CCG specific and utilise very different approaches. Varying combinations of risk factors, non-invasive fibrosis markers, liver blood tests, ultrasound, transient elastography and other tests have been used to determine how patients should be managed and who should be referred. The HSE data presented here suggest that a combination of risk factors and non-invasive fibrosis markers could be used to achieve a more inclusive starting point for risk stratification algorithms. Some evidence suggests this approach is likely to improve diagnostic yield and may be cost-effective.[54 158 159] Further evidence to inform national guidelines on the best approach to detecting liver disease in the general population is still needed.

Secondary prevention measures require not only identifying early disease in the population, but action to prevent or delay further progression. Many of these measures will be the same as those described for primary prevention, to reduce alcohol consumption and BMI. Weight loss has been shown to improve histological features in NAFLD patients, and physical activity has also been shown to reduce steatosis of the liver, even if weight loss is not achieved.[160 161] These are both recommended in clinical guidelines, but there are no equivalent guidelines for BAFLD as the group is not recognised.[103 104]

Liver fibrosis may be reversible, particularly in the early stages, when reduction of exposure to risk factors may be sufficient to achieve this. New anti-fibrotic drugs are being developed, which target different elements in the pathophysiology of chronic liver disease. These have the potential to reduce fibrosis, and therefore delay the development of cirrhosis.[162] Identifying those who will benefit most from these drugs will be important. The next decade will show to what extent these drugs may change the approach to secondary prevention, treatment and management of chronic liver disease.

5.4 Both Alcohol and Fatty Liver Disease (BAFLD)

A key output of this work has been the identification of this group of people as being at significantly increased risk of liver disease, and of further describing this group by sociodemographic and socioeconomic factors. Quantifying this group has been helpful in

demonstrating the size of the problem. The author has suggested the term 'BAFLD' to describe this group, as they are at risk from **B**oth **A**lcohol and **F**atty **L**iver **D**isease.

The delineation of 'Non-alcoholic fatty liver disease' and 'Alcoholic Liver Disease' may have led to neglect of the BAFLD group described above. This estimated 16% of the general population have a combination of increased BMI and alcohol risk factors, and therefore do not fit neatly in either NAFLD or ARLD groups. Referral criteria, from primary care to hepatology services, have tended to focus on assigning people to either NAFLD (drinking less than 14 units/week) or ARLD (drinking more than 35 units/week for women, 50 units/week for men) pathways. In the HSE sample, 80% of the BAFLD group (13% of the general population sample), were drinking more than recommended limits of alcohol but not enough to meet the ARLD criteria. They therefore did not meet standard referral criteria for either NAFLD or ARLD.

The end result of liver disease is a common pathway, regardless of its aetiology: Progression through stages of fibrosis and ultimately cirrhosis, with some also developing hepatocellular carcinoma. However, recognition of aetiology is absolutely essential for preventative strategies. Failure to properly recognise the BAFLD group of patients has led to their care being compromised on two levels. Firstly, many commonly used risk algorithms have not been designed to identify this group, so they may not be deemed at risk. Secondly, many referral pathways have not been designed for the BAFLD group, leaving GPs with difficulty accessing secondary care services for these patients.

British Society of Gastroenterology (BSG) guidelines report the existence of synergy between alcohol consumption and obesity, such that "when body mass index (BMI) is >35, the risk of liver disease doubles for any given alcohol intake".[58] Despite this, the guidelines offer separate NAFLD or ARLD algorithms to follow, depending on what the 'main' insult is considered to be.[58] The Royal College of General Practitioners' online liver disease toolkit[163] was designed to provide easy access to guidelines and tools for GPs. However, the information resources for practitioners, and the fact sheets for patients, were presented as separate ARLD and NAFLD fact sheets. No information was provided on the increased risk of liver disease for the BAFLD group of patients. National Institute for Health and Care Excellence guidance has also not been helpful regarding BAFLD patients. NICE NAFLD guidelines stated "take an alcohol history to rule out alcohol-related liver disease", but no alcohol consumption criteria for this were suggested.[104] They then recommend using the ELF® test for assessment of advanced fibrosis in patients with NAFLD.[104] In contrast to this, the NICE cirrhosis guidelines recommended offering transient elastography to people drinking >35 units/week (women) or >50 units/week (men).[105] With polarised recommendations for the assessment of advanced fibrosis/cirrhosis in NAFLD and ARLD patients,

there was no clarity on how to diagnose, assess or manage the BAFLD patients who fell between these two groups.

The author has not suggested the term 'BAFLD' with any desire to create further silos within liver disease, given how unhelpful the current delineations are. However, this group must be recognised so that they are appropriately risk stratified, assessed and managed within liver disease care pathways.

5.5 Strengths and Limitations

All the datasets analysed in this thesis were from general population settings, enabling expansion of knowledge in this important setting for prevention and early detection of liver disease. The datasets used in each element of this thesis were large, which allowed for robust estimates with relatively narrow parameters to be calculated. The meta-analysis included data from more than one million participants; the HSE dataset included data from nearly 8,000 participants and the NDNS dataset included data from nearly 7,000 participants. The HSE and NDNS surveys are both annual, national surveys conducted by the National Centre for Social Research. Their methods are well validated, and they provide survey weighting variables which allowed survey estimation techniques to be used in all statistical analyses. This means that the estimates derived from the samples, with weightings correctly applied, were highly likely to reflect the true situation in the general population of the UK. Both surveys also provide a large number of sociodemographic and socioeconomic information about participants, which is helpful in further delineating and describing sub-populations. One limitation was that only participants in private households were surveyed, so these results will not apply to those in other settings such as prisons, hospitals or residential care settings.

The meta-analysis included data provided directly by authors and from studies whose primary outcomes were not the same as investigated here. This meant that risk of publication bias was low, and a wider range of data than were available in the published literature could be included. Unfortunately only count data were available, and it was not possible to obtain individual participant data which would have allowed for adjustment by other variables.

There were several novel elements to this work, which have added value. The meta-analysis was the first to investigate risk of liver disease with combinations of alcohol and BMI risk factors. The HSE 2016 was the first (and only) time that liver function blood tests have been sampled in a general population setting in the UK. The ability to accurately calculate calories from alcoholic beverages, including mixers, in the NDNS diary data was novel.

Limitations are discussed in individual chapters in detail. All data were observational and therefore no conclusions about causal relationship can be made. The HSE and NDNS data were also cross-sectional, with no follow up of participants over time. The HSE and NDNS samples are entirely UK based, and the studies included in the meta-analysis came from the USA and Europe. It is important to remember that these findings may not be generalisable to other global populations, although that was not the aim of the work.

5.5.1 Alcohol data challenges

A significant problem which arose throughout this work, was the poor recording of alcohol consumption data. This is discussed in more detail, as it had an impact on each of the main elements of work in this thesis. Quality of alcohol data continues to have an impact on most alcohol research, and has frequently been raised with the author as a concern by those working in the field, such as alcohol specialist nurses, hepatology doctors and nurses and other researchers. The author has learned to be extremely careful to ascertain exactly what methods were employed in alcohol data collection, manipulation and presentation in research, before interpreting those data.

5.5.2 Quantifiable data

During the systematic review and meta-analysis work, a number of studies had to be excluded at the full text review stage, because the alcohol data provided were not detailed enough for further analysis. For example, one study categorised participants as alcohol consumers if they reported drinking 4 drinks per week or more and non-consumers if less.[164] There were many other studies that also used this method, where the categorisation of participants as alcohol drinkers or non-drinkers was binary, based on a seemingly arbitrary quantity of alcohol. These categorisations did not provide enough information to separate out different levels of alcohol consumption. In addition, there was no consistency across studies as to where the yes/no cut off was made.

5.5.3 Non-drinkers

The categorisation of ‘non-drinkers’ was also very inconsistent across the literature. Getting this reference group right is absolutely crucial in any research about alcohol consumption.[165] A J-shaped relationship has consistently been reported, between alcohol consumption and mortality, such that those consuming some alcohol are reported to have better mortality outcomes than those consuming no alcohol. However, the precise definition of the ‘no alcohol’ group is clearly

highly influential on any observed associations. It has been argued that participants who report zero alcohol consumption at the time of asking, may include ex-drinkers who have stopped drinking alcohol for reasons unknown but which may relate to their health.[166] The Million Women study investigated this group in detail, and found that only one in seven women who reported zero alcohol consumption were lifelong non-drinkers.[69] People who previously drank alcohol but have stopped, are likely to differ from both current consumers of alcohol, and lifetime abstainers, in ways that are difficult to measure but may influence their health outcomes.[69] In the same way, lifetime abstainers from alcohol have been shown to have significantly higher rates of illness, compared to those who consume alcohol at any level.[167] Misclassification of the reference group of abstainers has been shown to systematically alter the results of a wide research base.[168]

Alcohol consumption also changes over time. Overall, intake tends to reduce with increasing age.[165 168 169] Alcohol consumption questions are often asked only at baseline, and changes in consumption over time cannot therefore be accounted for.

More recently, Mendelian randomisation approaches and new methodologies have enhanced our understanding of the relationship between alcohol consumption and morbidity/mortality.[168-170] Results from a number of high quality studies now suggest that the J-shaped relationship between alcohol consumption and mortality may be due to misclassification bias and confounding, and that reduction in alcohol consumption at all levels, is beneficial for health.[169-171] A systematic analysis of The Global Burden of Disease study 2016 reports that the level of alcohol consumption that minimises harm across all health outcomes is zero.[172] This new understanding has emerged after decades in which there was believed to be a protective effect of moderate alcohol consumption on health, particularly cardiovascular disease.

Establishing a valid reference group for this research was therefore of critical importance to the researcher, and presented a significant challenge. Although the need to categorise participants carefully, to avoid misclassification bias, was very clear, many datasets did not contain enough information to allow this. Participants were usually categorised as ‘drinkers’ or ‘non-drinkers’ from their responses to questions asked about alcohol consumption. This categorisation was therefore dependent on the question asked, and these varied considerably between studies. The importance of the question asked was illustrated by the NDNS survey data. Depending on which alcohol question was used, the number of non-drinkers varied substantially (Table 35).

Table 35: Number of 'non-drinkers' identified by using different methods in the NDNS survey data years 1-9

Question / method	**Answer**	**Number of 'non-drinkers' identified (weighted count)**
Do you ever drink alcohol nowadays, including drinks you brew or make at home?	No	1494
Could I just check, does that mean you never have an alcoholic drink nowadays, or do you have an alcoholic drink very occasionally, perhaps for medicinal purposes or on special occasions like Christmas and New Year?	Never	799
Have you always been a non-drinker or did you stop drinking for some reason?	Always Stopped	799 0
Frequency drank any alcohol over last 12 months	Not at all / never	934
Answered 'not at all/ never' to question about frequency of alcohol consumption over last 12 months AND did not drink any alcohol during diary days.		916

Some well-regarded studies have excluded from their analysis all participants who reported drinking zero alcohol, due to the heterogeneity of this group.[69] This method reduces the concern that misclassification bias will affect the results, in situations where adequate data to accurately classify participants' alcohol consumption, with sufficient granularity, are not available. This approach was employed in our meta-analysis (Chapter two), as many of the included studies collected only baseline alcohol consumption data, without further detail on changes in consumption over the participants' lifetime.

5.5.4 Self-reporting

All alcohol data from the studies analysed in this thesis were self-reported, via either questionnaire or interview. Self-reporting of any data leaves researchers open to the criticism that it could be inaccurate, leading to concerns about the interpretation of results. On balance, the literature concludes that self-reporting of alcohol consumption is sufficiently valid and reliable for research purposes.[173 174] As with any research, the quality of design and execution of study methods is paramount. The chances of mis-reporting vary, depending on the characteristics of the participants, the interview location and context, and how the information is requested.[174] These factors can all be minimised by optimising research techniques, for example how assurances are given of the anonymity/confidentiality of responses.[173] There remains a need for greater understanding about specific groups and situations in which mis-reporting may occur.[175]

The NDNS and HSE survey data analysed here are of a highly reproducible method and reliable execution. Full details of the survey methods used are available.[94 127-130] Pictures of glass sizes are provided, to help participants to accurately report their intake, and different strengths of beer are presented as options to enable accurate calculation of alcohol content (Appendix B, Appendix C). For studies included in the systematic review and meta-analysis, the level of detail about methods used varied. This made it difficult to assess any likely biases. The quality assessment tool used did not examine in detail the interview techniques applied in each study. As discussed, these might have affected the reliability and validity of responses.

5.5.5 Categorical data

Where studies did collect quantifiable information about alcohol consumption, this was in every case presented as categorical, not continuous data. The cut-off points between different categories were not consistent across studies and this led to difficulties combining data and comparing like for like. In most cases, the data had been collected as categorical data, so it was not possible to go back to the original data and re-define categories. For research to be valuable, alcohol consumption data should ideally be collected as a continuous variable. Data could then be analysed as a continuous variable, or re-categorised as per the requirements of the researcher. This would facilitate greater understanding of the true nature of relationships between other variables and alcohol consumption. For example, the meta-analysis presented in chapter two would have been able to show at what level of alcohol consumption risk starts to increase, whether there are step changes in risk and whether risk plateaus at any level of consumption. BMI data were usually collected as a continuous variable, but presented categorically in published

studies. The categories used were consistent across studies, which allowed for accurate comparisons, although ethnic-specific categories were not generally used. If the original continuous data on BMI were made available to researchers, the scope of research would be greatly enhanced. For example, the meta-analysis presented in chapter two would have had the ability to determine step changes in risk at certain levels of BMI.

In studies from the UK, measures of alcohol were reported in units, with one unit equivalent to eight grams of pure ethanol. In studies from the USA and other countries, alcohol was measured directly in grams. Conversion of grams to units and vice-versa was simple enough. However, data were presented categorically and the categories used did not readily equate. Studies from the UK tended to categorise above and below the recommended limit of alcohol consumption, which the UK Chief Medical Officers currently identify as 14 units per week. Studies from elsewhere used categories of alcohol consumption in grams, which did not correspond to the UK categories.

5.5.6 Weekly consumption estimates

Alcohol consumption questions asking about consumption per day, were difficult to interpret. It was not possible to know if the responses were considered to reflect an 'average' day for the participant. Some questions specifically asked about consumption on the 'heaviest drinking day' during the previous week. Responses to these types of questions about daily consumption cannot reasonably be multiplied up to obtain a weekly estimate. From the NDNS data presented here, it is clear that for the majority of participants, alcohol consumption varied significantly from day to day. It is therefore hard to see the usefulness of daily consumption data, for any period less than one week. Longer periods of time are likely to provide a more accurate reflection of true alcohol consumption patterns.

The HSE and NDNS surveys both provide many 'derived' variables in the dataset, which have been calculated from the original data collected. One of these is participants' weekly alcohol consumption in units. Participants were asked how often, over the last 12 months, they had consumed each different type of alcoholic drink (normal beer/cider, strong beer/cider, wine, sherry, spirits, alcopops). Options for frequency ranged from 'Almost every day' to 'Not at all in last 12 months'. Participants were then asked how much of the drink they usually consumed, on days they drank it. The answers to these two questions were combined by the survey team, to provide a derived variable which is detailed as participants' usual weekly alcohol consumption. The questions used do not allow participants to express variations in alcohol consumption, and the weekly units calculated can only be a very rough approximation of intake. It is hard to know

whether the calculation will over or under estimate consumption to an equal degree for all participants. It is likely to be more accurate for those whose consumption is regular and predictable.

The NDNS food and beverage diary would have been an excellent resource for studying variations in alcohol consumption patterns over the week, and could have provided a more accurate weekly consumption figure. However, the diary was only three or four days long. Extrapolating these data to provide an estimate of weekly consumption was challenging and could only reasonably be achieved for a small subgroup.

The weekly consumption estimates in the HSE and NDNS provide an approximation of consumption that is useful, and no criticism of the methods used to derive them is intended. The problem lies with the original data, which are simply inadequate to calculate accurate weekly alcohol consumption.

5.5.7 Recommendations

To be effective for research, alcohol consumption needs to be recorded with as much detail as possible. Self-reporting is pragmatic but its validity is dependent on robust methodology.[174] Routinely checking a small subset for accuracy would be helpful to expand our knowledge about under/over reporting in different groups. The NDNS has used a Doubly Labelled Water technique to investigate under-reporting of food calories in this way. Where possible, the exact amount of alcohol consumed, in grams or units, should be recorded. A seven day food and beverage diary would allow for a more accurate assessment of true weekly intake. Ideally two or three weeks over the period of a few months would be sampled, to assess consistency of response, and to capture less routine consumption.

Alongside any quantitative measurements, a set of qualitative questions needs to be included, to elicit enough information to accurately categorise consumption for analysis. For example, there are difficulties characterising ‘non-drinkers’ as described above. Alcohol consumption is not a simple, predictable or consistent habit for many people. The list of factors that may influence alcohol consumption is almost endless. Some, such as religion, culture and genetic factors are more stable influences. Others are subject to frequent change: working patterns, income, timing of receipt of income, holidays, parenting, social engagements, living arrangements, age, special occasions, relationships, bereavement, mental health issues and physical health issues may all have an impact. This list is not exhaustive. For data to be meaningful, collection therefore needs

to attempt, however difficult it may be, to capture the complex nature of consumption. There is much to be done in improving alcohol consumption data for research purposes. Without improvement, we risk making false conclusions based on flawed data, as evidenced by the 'J-shaped curve' phenomenon previously described.

5.6 Next steps, future work

The implications of the findings presented in this thesis, and suggestions for policy, practice and future research have been addressed throughout this discussion. On a personal level, the author is passionate about the prevention and early detection of liver disease, in order to improve outcomes for patients. Her wish is to be able to translate this research in to clinical practice, for the benefit of all those at risk of liver disease, or who have early disease. She has planned future work with the hope of achieving this.

The author has arranged to work with the hepatology department of an NHS hospital trust, and the Clinical Commissioning Group (CCG), to collaborate with them in designing a new risk stratification algorithm. This will be used in primary care, to help general practitioners identify those at risk of liver disease who need to be referred to secondary care hepatology services, and those who can be safely managed in primary care. An existing algorithm is in place, which uses the NAFLD fibrosis score, and referral pathways are therefore limited to patients drinking less than 14 units of alcohol per week. As this thesis has shown, there is significant liver risk in overweight and obese patients drinking more than 14 units per week, and this will be reflected in the new algorithm. The algorithm will use a combination of risk factors and non-invasive liver function tests. The results of this thesis will inform the algorithm.

New pathways into care will be created as a result of using the algorithm, for example for BAFLD patients, and this may result in changes to demand for secondary care clinics. The author will use data from a local joint database of primary and secondary care data (the Hampshire Health Record), to model predicted changes in patient flows which may occur as a result of the new risk algorithm and referral pathways. It will be possible to run different scenarios within this modelling, to ensure that services will not be overwhelmed.

When the new risk algorithm and referral pathways are launched, the author plans to conduct a service evaluation, to assess the impact of changes made. Learning from this will be disseminated locally, and submitted for publication to peer-reviewed journals.

The author will also analyse new data in collaboration with the British Liver Trust (BLT). The BLT run community screening for liver disease in their mobile van, touring the UK. Anyone may approach the van, complete a liver risk screening tool online, and then have a Fibroscan®. The BLT have kindly shared anonymous data in which risk factor profiles are linked to the Fibroscan® result of that person. This will provide valuable outcome data, related to risk factors, as Fibroscan® is a physical measurement of liver stiffness and is considered more accurate than the non-invasive tests that it was possible to explore in this thesis.

As anyone can approach the van for assessment, these data are likely to reflect significant ascertainment bias and they will need to be interpreted carefully. We would not be able to generalise from these results to the wider population, however the associations between risk factor profiles and Fibroscan® results at an individual level will still provide useful information. The author hopes that this collaboration will be the starting point for further work with the BLT, particularly Patient and Participant Involvement (PPI) work to shape future research.

Appendices

Appendix A

A.1 Newcastle-Ottawa quality assessment scale for cohort studies (customised)

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE COHORT STUDIES (customised)

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

Selection

1) Representativeness of the exposed cohort

Item is assessing the representativeness of exposed individuals in the community, not the representativeness of the sample from some general population. However, in our case our 'community' is the general population, so we should assess here the representativeness of exposed individuals to the general population.

a) exposed individuals are truly representative of the average person in the general population ✵
b) somewhat representative of the average person in the general population ✵
c) selected group e.g. nurses, volunteers, pregnant, HBV+ve
d) no description of the derivation of the cohort

2) Selection of the non exposed cohort

a) drawn from the same community as the exposed cohort ✵
b) drawn from a different source
c) no description of the derivation of the non exposed cohort

3) Ascertainment of exposure

a) secure record (eg surgical records) ✵
b) structured interview ✵
c) written self report
d) no description

4) Demonstration that outcome of interest was not present at start of study

a) yes ✵
b) no

Comparability

1) Comparability of cohorts on the basis of the design or analysis
   a) study controls for age and sex ✸
   b) study controls for social class or smoking or diabetes ✸

Outcome

1) Assessment of outcome
   a) independent blind assessment ✸
   b) record linkage ✸
   c) self report
   d) no description

2) Was follow-up long enough for outcomes to occur
   a) yes (10 years) ✸
   b) no

3) Adequacy of follow up of cohorts
   a) complete follow up - all subjects accounted for ✸
   b) subjects lost to follow up unlikely to introduce bias - small number lost - > 80% follow up, or description provided of those lost ✸
   c) follow up rate < 80% and no description of those lost
   d) no statement

A.2 Baseline data for the seven cohort studies which were not included in the meta-analysis (data not available)

Table 36 Appendix: Baseline data for the seven cohort studies which were not included in the meta-analysis

Author	Year	Country	Sample & setting	Participants	Gender	Age	Ethnicity	Follow up duration†	Follow up method
Fuchs[176]	1995	USA	Registered female nurses.	85,709	Female	30-55yrs	No information	12yrs	Record linkage with National Death index.
Goh[177]	2014	Singapore	General population residing in government-built housing estates.	63,275	44·2% male	45-74yrs	Singaporean Chinese	Mean 14·7yrs	Record linkage with Registry of Deaths and cancer registry.
Ioannou[80]	2003	USA	General population cohort.	11,465	38·7% Male	25-74yrs	84·2% Caucasian	Mean 12·9yrs	Subjects or proxies interviewed again, death certificates obtained for those who had died, and nursing home / hospital records obtained for overnight stays.
Jee[178]	2004	Korea	Insured government workers and their dependents.	1,283,112	63·7% male	30-95yrs	No information	Median 10yrs	Record linkage to death certificate data.
Klatsky[179]	2006	USA	General population cohort who have health insurance.	125,580	44% male	71% <50yrs 15% 50-59yrs 14% ≥60yrs	55% white 27% black 11% Asian 4% Hispanic 2% other	Mean 14·1yrs	Record linkage.
Michikawa[180]	2012	Japan	General population cohort.	17,654	35% male	40-69yrs	No information	Mean 12·6yrs	Data linkage with cancer registries. Death certificates. Notifications from hospitals in study area.
Thun[181]	1997	USA	General population cohort, recruited by volunteers.	489,626	42·7% female	30-104yrs	94% white	9yrs	Record linkage and death certificates.

† Median or mean follow-up duration if stated

USA – United States of America, HCC – Hepatocellular Carcinoma

A.3 Exposure and outcome summary data for the seven cohort studies which were not included in the meta-analysis

Table 37 Appendix: Exposure and outcome summary data for the seven cohort studies which were not included in the meta-analysis

Author	Year	Total cases	Liver outcome	BMI assessment	BMI<25	BMI 25 to <30	BMI≥30	Alcohol assessment	Alcohol zero	Alcohol within UK limits† >0 to 14 units/week	Alcohol above UK limits† ≥15 units/week
Fuchs[176]	1995	2658 (3·1%)	Cirrhosis mortality	Self-reported	No information			Food frequency questionnaire	29·8%	55·5% <15g/day	14·7% ≥15g/day
Goh[177]	2014	114 (0·18%)	Cirrhosis mortality	Self-reported	78·2%	21·8% BMI ≥25		Food frequency questionnaire	81·2%	16·2% <20g/day	2·5% ≥20g/day
Ioannou[80]	2003	89 (0·8%)	Cirrhosis hospitalisation or mortality	Measured	50·2%	32·9%	16·9%	24 hr recall food and beverage consumption survey	41·5%	52·8% ≤ 2 drinks/day	5·7% >2 drinks/day
Jee[178]	2004	3807 (0·30%)	HCC mortality	Not specified	Mean BMI 23·2			Self-reported	Mean 17·2g/day men, 0·2g/day women		
Klatsky[179]	2006	330 (0·26%)	Cirrhosis hospitalisation or mortality	Measured	No information			Self-reported	15·2%	75·8% ≤ 2 drinks/day	8·0% ≥ 3 drinks/day
Michikawa[180]	2012	104 (0·59%)	HCC incidence	Measured	77·8%	22·2% BMI ≥25		Self-reported	63·6%	21·4% <150g/week	15·1% ≥150g/week
Thun[181]	1997	Not available	Cirrhosis, alcoholism or both - mortality	Not specified	Mean 25·2			Self-reported	33·3%	40·3% 1 drink/day	26·5% ≥ 2 drinks/day

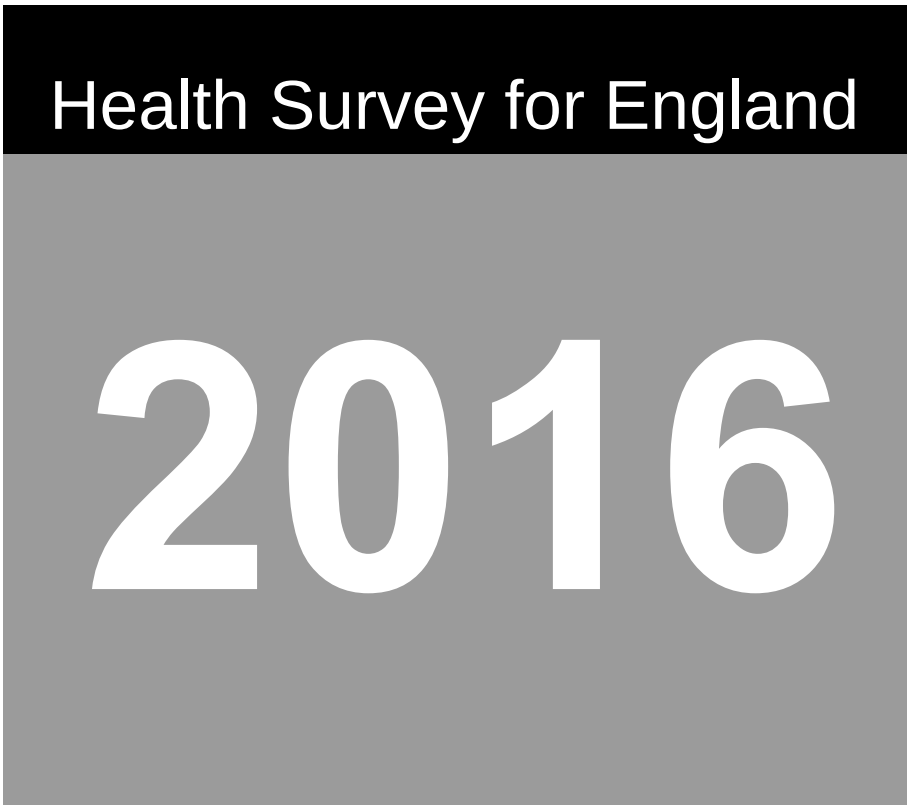
† Assumes 1 drink = 2 units = 16 grams of alcohol

HCC – Hepatocellular Carcinoma, CLD – Chronic Liver Disease, BMI – Body Mass Index

Appendix B

B.1 Alcohol related interview questions used in the Health Survey for England (HSE) 2016

UK Data Archive Study Number 8334 - Health Survey for England, 2016



Questionnaires and showcards

Drinking (Aged 18+)

[IF (Age of Respondent is 25 years or over) OR (BookChk = Asked)] Drink

I am now going to ask you a few questions about what you drink - that is if you drink. Do you ever drink alcohol nowadays, including drinks you brew or make at home?

1 Yes
2 No

[IF Drink = No] DrinkAny

Could I just check, does that mean you never have an alcoholic drink nowadays, or do you have an alcoholic drink very occasionally, perhaps for medicinal purposes or on special occasions like Christmas and New Year?

1 Very occasionally
2 Never

[IF DrinkAny = Never]
AlwaysTT

Have you always been a non-drinker or did you stop drinking for some reason?

1 Always a non-drinker
2 Used to drink but stopped

[IF AlwaysTT = Used to drink but stopped] WhyTT

Did you stop drinking because of a particular health condition that you had at the time?
INTERVIEWER: If respondent says pregnancy, code Yes.

1 Yes
2 No

[IF (Drink = Yes) OR (DrinkAny = very occasionally)] DrinkOft

SHOW CARD I1
Thinking now about all kinds of drinks, how often have you had an alcoholic drink of any kind during the last 12 months?

1 Almost every day
2 Five or six days a week
3 Three or four days a week
4 Once or twice a week
5 Once or twice a month
6 Once every couple of months
7 Once or twice a year
8 Not at all in the last 12 months

[IF DrinkOft <> Not at all in the last 12 months]
DrinkL7

Did you have an alcoholic drink in the seven days ending yesterday?

1 Yes
2 No

[IF DrinkL7 =Yes] DrnkDay

On how many days out of the last seven did you have an alcoholic drink?

Range: 1..7

[IF DrnkDay = 2 to 7 days]
DrnkSame

Did you drink more on *one of the days/some days than others*, or did you drink about the same on *both/each of those* days?

1 Drank more on one/some day(s) than other(s)
2 Same each day

WhichDay
Which day *last week* did you *last have an alcoholic drink/have the **most** to drink*?

1 Sunday
2 Monday
3 Tuesday
4 Wednesday
5 Thursday
6 Friday
7 Saturday

DrnkType
SHOW CARD I2
Thinking about last *(answer to WhichDay)*, what types of drink did you have that day? CODE ALL THAT APPLY

1 Normal strength beer/lager/stout/cider/shandy
2 Strong beer/lager/stout/cider
3 Spirits or liqueurs
4 Sherry or martini
5 Wine
6 Alcopops/pre-mixed alcoholic drinks
7 Other alcoholic drinks
8 Low alcohol drinks only

[IF DrnkType = Normal strength beer/lager/cider/shandy] NBrL7
Still thinking about last *(answer to WhichDay)*, how much **normal strength beer, lager, stout, cider or shandy** (excluding cans and bottles of shandy) did you drink that day? INTERVIEWER: Code measures that you are going to use..

1 Half pints
2 Small cans
3 Large cans
4 Bottles

[IF NBRL7=Half pints]
NBrL7Q(1)
ASK OR CODE: How many half pints of **normal strength beer, lager, stout, cider or shandy** *(excluding cans and bottles of shandy)* did you drink that day?

Range: 1..97

[IF NBrL7Q = Small cans]
NBrL7Q(2)
ASK OR CODE: How many small cans of **normal strength beer, lager, stout, cider or shandy** did you drink that day?

Range: 1..97

[IF NBrL7=Large cans]
NBrL7Q(3)
ASK OR CODE: How many large cans of **normal strength beer, lager, stout, cider or shandy** did you drink that day?

Range: 1..97

[IF NBrL7=Bottles]
NBrL7Q(4)
ASK OR CODE: How many bottles of **normal strength beer, lager, cider or shandy** did you drink that day?
Range: 1..97

NBotL7
ASK OR CODE: What make of **normal strength beer, lager, stout, cider or shandy** did you drink from bottles on that day? INTERVIEWER: IF RESPONDENT DRANK DIFFERENT MAKES CODE WHICH THEY DRANK MOST.
Text: Maximum 21 characters

[IF DrnkType = Strong beer/lager/cider] SBrL7
Still thinking about last *(answer to WhichDay)*, how much **strong beer, lager, stout or cider** did you drink that day? INTERVIEWER: CODE MEASURES THAT YOU ARE GOING TO USE.

1 Half pints
2 Small cans
3 Large cans
4 Bottles

[IF SBRL7=Half pints] SBrL7Q(1)
ASK OR CODE: How many half pints of **strong beer, lager, stout or cider** did you drink on that day?
Range: 1..97

[IF SBrL7=Small cans] SBrL7Q(2)
ASK OR CODE: How many small cans of **strong beer, lager, stout or cider** did you drink on that day?
Range: 1..97

[IF SBrL7=Large cans] SBrL7Q(3)
ASK OR CODE: How many large cans of strong beer, lager, stout or cider did you drink on that day?
Range: 1..97

[IF SBrL7=Bottles]
SBrL7Q(4)
ASK OR CODE: How many bottles of strong beer, lager, stout or cider did you drink on that day?
Range: 1..97

SBotL7
ASK OR CODE: What make of **strong beer, lager, stout or cider** did you drink from bottles on that day? INTERVIEWER: IF RESPONDENT DRANK DIFFERENT MAKES CODE WHICH THEY DRANK MOST
Text: Maximum 21 characters

[IF DrnkType = Spirits]

SpirL7

Still thinking about last *(answer to WhichDay),* how much spirits or liqueurs (such as gin, whisky, brandy, rum, vodka, advocaat or cocktails) did you drink on that day?

Code the number of singles – count doubles as two singles.

Range: 1..97

[IF DrnkType = Sherry] ShryL7

Still thinking about last *(answer to WhichDay)*, how much sherry or martini, including port, vermouth, Cinzano and Dubonnet did you drink on that day? INTERVIEWER: Code the number of glasses.

Range: 1..97

[IF DrnkType = Wine] WineL7

Still thinking about last *(answer to WhichDay)*, how much wine, including Babycham and champagne, did you drink on that day?

INTERVIEWER: Code the measure the respondent used.

Please note that respondent may give answer in bottles and glasses. Please code the relevant option.

1 Bottle or parts of bottle
2 Glasses
3 Both bottles or parts of bottle, and glasses

[IF WineL7= 1 (Bottles or part of bottle)] WL7Bt

INTERVIEWER: Code the number of 125ml glasses drunk **from the bottle** by the respondent. E.g. If they drank half a bottle, code 3 glasses. Press <F9> for information

CODE THE NUMBER OF GLASSES. 1
BOTTLE =6 GLASSES
½ BOTTLE=3 GLASSES 1/3
BOTTLE=2 GLASSES
¼ BOTTLE=1.5 GLASSES

1 LITRE =8 GLASSES
½ LITRE=4 GLASSES 1/3
LITRE=2.5 GLASSES
¼ LITRE=2 GLASSES

Range: 1..97 (ALLOW FRACTIONS)

F9 for WL7Bt

If respondent has answered in bottles or litres convert to glasses using the information provided on the screen. For example if a respondents said they shared a bottle with one other person and they shared it equally code 3 glasses.

[IF WineL7= 2 (Glasses)] WL7Gl

INTERVIEWER: Code the number of glasses **(drunk as glasses).**

Range: 1..97 (ALLOW FRACTIONS)

WL7Glz

SHOWCARD L3 [Picture of WGls125ml, WGls175ml, WGls250ml] Were you drinking from a large, standard or small glass?

INTERVIEWER: If respondent drank from two or three different size glasses, please code all that apply.

INTERVIEWER: please note that if respondent was drinking in a pub or wine bar and had a small glass, this would usually be 175ml.

1. Large glass (250mL)
2. Standard glass (175 mL)
3. Small glass (125 mL)

[IF WL7Glz=1 and other]
ml250Glz
How many large glasses (250 ml) did you drink?

[IF WL7Glz=2 and other]
ml175mGlzl
How many standard glasses (175 ml) did you drink?

[IF WL7Glz=3 and other]
ml125Glz
How many small glasses (125 ml) did you drink?

[IF DrnkType = Alcopops/pre-mixed alcoholic drink] PopsL711
Still thinking about last *(answer to WhichDay)*, how much **alcoholic soft drink** ('alcopop') did you drink on that day? INTERVIEWER: CODE MEASURES THAT YOU ARE GOING TO USE

1 Small cans
2 Standard Bottles (275ml)
3 Large Bottles (700ML)

[IF PopsL711 = Small cans]
PopsL7Q(1)
ASK OR CODE: How many small cans of alcoholic soft drink ('alcopop') did you drink on that day?
Range: 1..97

[IF PopsL7= standard sized Bottles]
PopsL7Q(2)
ASK OR CODE: How many standard bottles of alcoholic soft drink ('alcopop') did you drink on that day?:
Range: 1..97

[IF PopsL7= LargeBottles]
PopsL7Q(3)
ASK OR CODE: How many large bottles of alcoholic soft drink ('alcopop') did you drink on that day?:
Range: 1..97

[IF DrnkType=Other]
OthL7TA
Still thinking about last *(answer to WhichDay)*, what other type of alcoholic drink did you drink on that day? Code first mentioned only.
Text: Maximum 30 characters

OthL7QA
How much *(name of 'other' alcoholic drink)* did you drink on that day?
INTERVIEWER: Write in how much. Remember to specify half pints/ singles/ glasses/ bottles.
Text: Maximum 30 characters

OthL7B

Did you drink any other type of alcoholic drink on that day?

1 Yes
2 No

[IF OthL7B=Yes]
OthL7TB
Still thinking about last *(answer to WhichDay)*, what other type of alcoholic drink did you drink on that day? Code first mentioned only.

Text: Maximum 30 characters

OthL7QB
How much *(name of 'other' alcoholic drink)* did you drink on that day?
INTERVIEWER: Write in how much. Remember to specify half pints/ singles/ glasses/ bottles.

Text: Maximum 30 characters

OthL7C
Did you drink any other type of alcoholic drink on that day?

1 Yes
2 No

[IF OthL7C=Yes]
OthL7TC
Still thinking about last *(answer to WhichDay)*, what other type of alcoholic drink did you drink on that day?
Code first mentioned only.

OthL7QC
How much *(name of 'other' alcoholic drink)* did you drink on that day?

INTERVIEWER: Write in how much. Remember to specify half pints/ singles/ glasses/ bottles. Text: Maximum 30 characters

DrAmount
Compared to five years ago, would you say that on the whole you drink more, about the same or less nowadays?

1 More nowadays
2 About the same
3 Less nowadays

ENDIF
ENDIF

[IF Drink = 1 or DrinkAny = 1] Intro
I'd like to ask you whether you have drunk different types of alcoholic drink in the **last 12 months**. I'd like to hear about ALL types of alcoholic drinks you have had.

If you are not sure whether a drink you have had goes into a category, please let me know. I do not need to know about non-alcoholic or low alcohol drinks.
INTERVIEWER: PRESS <F9> AT FOLLOWING QUESTIONS FOR MORE INFORMATION ABOUT WHAT SHOULD BE INCLUDED AT THE DIFFERENT DRINKS CATEGORIES.

NBeer
SHOWCARD I1
I'd like to ask you first about normal strength beer, lager, stout, cider or shandy which has less than 6% alcohol. How often have you had a drink of normal strength beer, lager, stout, cider **or** shandy (excluding cans and bottles of shandy) during the last 12 months?
(NORMAL = LESS THAN 6% ALCOHOL BY VOLUME.)

<F9> FOR INFO ON DRINKS TO BE INCLUDED HERE.

1 Almost every day
2 Five or six days a week
3 Three or four days a week
4 Once or twice a week
5 Once or twice a month
6 Once every couple of months
7 Once or twice a year
8 Not at all in last 12 months

[IF NBeer = 1 – 7]
NBeerM
How much NORMAL STRENGTH BEER, LAGER, STOUT, CIDER or SHANDY (excluding cans and bottles of shandy) have you usually drunk on any one day during the last 12 months?
INTERVIEWER: FIRST CODE TYPE OF MEASURE AND THEN CODE NUMBER OF EACH MEASURE. CODE ALL THAT APPLY.

1 Half pints
2 Small cans
3 Large cans
4 Bottles

[IF NBeerM=half pints / 2=small cans / 3=large cans / 4=bottles] NBeerQ
How many (half pints/ small cans/ large cans/ bottles) of NORMAL STRENGTH BEER, LAGER, STOUT, CIDER or SHANDY (excluding cans and bottles of shandy) have you usually drunk on any one day during the last 12 months?

Range 1..97

[IF Drinknow = 1 or DrinkAny = 1] SBeer
SHOWCARD I1
Now I'd like to ask you about STRONG BEER OR CIDER which has 6% or more alcohol (eg Tennant's Extra, Special Brew, Diamond White). How often have you had a drink of strong BEER, LAGER, STOUT or CIDER during the last 12 months? STRONG=6% AND OVER ALCOHOL BY VOLUME. USE HELP SCREEN FOR OTHER DRINKS TO BE INCLUDED HERE.

1 Almost every day
2 Five or six days a week
3 Three or Four days a week
4 Once or twice a week
5 Once or twice a month
6 Once every couple of months
7 Once or twice a year
8 Not at all in last 12 months

[IF SBeer = 1 – 7]
SBeerM
How much STRONG BEER, LAGER, STOUT or CIDER have you usually drunk on any one day during the last 12 months?
INTERVIEWER: FIRST CODE TYPE OF MEASURE AND THEN CODE NUMBER OF EACH MEASURE.

1 Half pints
2 Small cans
3 Large cans
4 Bottles

[IF SBeerM = 1 – 4]
SBeerQ

ASK OR RECORD, How many (half pints/ small cans/ large cans/ bottles) of STRONG BEER, LAGER, STOUT or CIDER have you usually drunk on any one day during the last 12 months?

Range: 1..97

[IF Drinknow = 1 or DrinkAny = 1] Spirits

SHOWCARD I1

How often have you had a drink of SPIRITS OR LIQUEURS, such as gin, whisky, brandy, rum, vodka, advocaat or cocktails during the last 12 months?

<F9> FOR OTHER DRINKS TO BE INCLUDED HERE.

1 Almost every day
2 Five or six days a week
3 Three or four days a week
4 Once or twice a week
5 Once or twice a month
6 Once every couple of months
7 Once or twice a year
8 Not at all in last 12 months

[IF Spirits = 1 – 7] SpritsQ

How much SPIRITS OR LIQUEURS, such as gin, whisky, brandy, rum, vodka, advocaat or cocktails have you usually drunk on any one day during the last 12 months? CODE THE NUMBER OF SINGLES -

Range: 1..97

[IF Drinknow = 1 or DrinkAny = 1] Sherry

SHOWCARD I1

How often have you had a drink of SHERRY OR MARTINI including port, vermouth, Cinzano and Dubonnet, during the last 12 months?

<F9> FOR OTHER DRINKS TO BE INCLUDED HERE.

1 Almost every day
2 Five or six days a week
3 Three or four days a week
4 Once or twice a week
5 Once or twice a month
6 Once every couple of months
7 Once or twice a year
8 Not at all in last 12 months

[IF Sherry = 1 – 7] SherryQ

How much SHERRY OR MARTINI, including port, vermouth, Cinzano and Dubonnet have you usually drunk on any one day during the last 12 months? CODE THE NUMBER OF GLASSES

Range: 1..97

[IF Drinknow = 1 or DrinkAny = 1] Wine

SHOWCARD I1

How often have you had a drink of WINE, including Babycham and champagne, during the last 12 months?

<F9> FOR OTHER DRINKS TO BE INCLUDED HERE.

1 Almost every day
2 Five or six days a week
3 Three or four days a week
4 Once or twice a week
5 Once or twice a month
6 Once every couple of months
7 Once or twice a year
8 Not at all in last 12 months

[IF Wine = 1 – 7]

WineQ
How much WINE, including Babycham and champagne, have you usually drunk on any one day during the last 12 months? CODE THE NUMBER OF GLASSES.

INTERVIEWER: code the number of 125ml glasses drunk **from the bottle** by the respondent. E.g. If they drank half a bottle, code 3 glasses. Press <F9> for information

CODE THE NUMBER OF GLASSES. 1 BOTTLE
=6 GLASSES
½ BOTTLE=3 GLASSES 1/3
BOTTLE=2 GLASSES
¼ BOTTLE=1.5 GLASSES

1 LITRE=8 GLASSES
½ LITRE=4 GLASSES 1/3
LITRE=2.5 GLASSES
¼ LITRE=2 GLASSES
Range: 1..97

BWineQ2
SHOW CARD I3
Were those mainly ...READ OUT…
INTERVIEWER: IF RESPONDENT USUALLY DRINKS IN A PUB OR WINE BAR AND HAD A SMALL GLASS, THIS WOULD USUALLY BE 175ML.

1 Small Glasses (approx. 125ml)
2 Standard (approx. 175ml)
3 Or Large Glasses (approx. 250ml)
4 Bottles (Spontaneous Only)

[IF Drinknow = 1 or DrinkAny = 1] Pops
SHOWCARD I1
How often have you had a drink of ALCOPOPS (i.e. alcoholic lemonade, alcoholic colas or other alcoholic fruit-or-herb-flavoured drinks for e.g. Smirnoff Ice, Bacardi Breezer, WKD, Metz etc), during the last 12 months?

1 Almost every day
2 Five or six days a week
3 Three or four days a week
4 Once or twice a week
5 Once or twice a month
6 Once every couple of months
7 Once or twice a year
8 Not at all in last 12 months

[IF Pops = 1 – 7]
PopsLY11
How much ALCOPOPS or pre-mixed alcoholic drinks (i.e. alcoholic lemonade, alcoholic colas or other alcoholic fruit-or-herb-flavoured drinks) have you usually drunk on any one day during the last 12 months?
INTERVIEWER: Code the measure(s) that you are going to use.

1 Small cans
2 Standard Bottles (275ml)

3 Large Bottles (700ml)

[IF PopsLY11 = Small cans] PopsQ11[1]
ASK OR CODE: How many small cans of alcoholic or pre-mixed drink have you usually drunkon any one day?

Range: 1..97

[IF PopsLY11=standard Bottles] PopsQ11[2]
ASK OR CODE: How many standard sized bottles of alcoholic or pre-mixed drink have youusually drunk on any one day?

Range: 1..97

[IF PopsLY11= large Bottles]
PopsQ11[3]
ASK OR CODE: How many large bottles of alcoholic or pre-mixed drink have you usually drunkon any one day?

Range: 1..97

Appendix B

HSE 2016

SHOWCARDS

1. **Almost every day**

2. **Five or six days a week**

3. **Three or four days a week**

4. **Once or twice a week**

5. **Once or twice a month**

6. **Once every couple of months**

7. **Once or twice a year**

8. **Not at all in the last twelve months**

1. **Normal strength beer, lager, stout, cider or shandy** (less than 6 % alcohol)

   (excluding cans or bottles of shandy)

2. **Strong beer, lager, stout or cider**
   (6% alcohol or more) (e.g. Tennents Super, Special Brew, Diamond White)

3. **Spirits or Liqueurs**
   (e.g. Gin, Whisky, Brandy, Rum, Vodka, Advocaat, Cocktails)

4. **Sherry or Martini** (including Port, Vermouth, Cinzano and Dubonnet)

5. **Wine** (including Babycham and Champagne)

6. **Alcoholic soft drinks, 'alcopops' or pre-mixed alcoholic drinks**

   (e.g. Bacardi Breezer, Metz or Smirnoff Ice)

7. **Other alcoholic drinks**

8. **Low alcohol drinks only**

B.2 Linear regression model for ALT and AST

Table 38: Univariate and age/sex adjusted linear regression model for ALT and AST

		ALT			AST		
		Weighted n	Univariate Coef (95%CI)	Age and sex adjusted Coef (95%CI)	Weighted n	Univariate OR (95%CI)	Age and sex adjusted OR (95%CI)
Age	Age, years	3607	-0.07 (-0.10, -0.04)**	-0.06 (-0.10, -0.03)**	3425	-0.02 (-0.04, -0.00)*	-0.02 (-0.04, -0.00)*
Sex	Male	3607	Ref	Ref	3425	Ref	Ref
	Female		-8.14 (-9.31, -6.96)**	-8.06 (-9.23, -6.89)**		-3.45 (-4.20, -2.70)**	-3.43 (-4.18, -2.69)**
Ethnicity	White	3601	Ref	Ref	3419	Ref	Ref
	Black		0.97 (-1.99, 3.93)	0.58 (-2.41, 3.58)		0.33 (-1.86, 2.51)	0.33 (-1.83, 2.48)
	Asian		3.05 (-0.18, 6.28)	2.55 (-0.54, 5.63)		0.55 (-0.92, 2.02)	0.44 (-1.03, 1.91)
	Mixed/multiple/Other		1.51 (-3.04, 6.06)	0.23 (-4.87, 5.32)		1.99 (-0.90, 4.89)	1.55 (-1.50, 4.60)
Index of multiple deprivation	Least deprived	3607	Ref	Ref	3425	Ref	Ref
	2nd		1.31 (-0.35, 2.98)	0.99 (-0.60, 2.59)		0.71 (-0.25, 1.66)	0.58 (-0.34, 1.51)
	3rd		0.55 (-0.95, 2.05)	-0.16 (-1.63, 1.31)		-0.30 (-1.30, 0.70)	-0.57 (-1.57, 0.43)
	4th		2.33 (0.28-4.38)*	1.31 (-0.62, 3.23)		0.93 (-0.43, 2.28)	0.56 (-0.73, 1.85)
	Most deprived		1.18 (-0.71, 3.08)	0.65 (-1.24, 2.53)		-0.09 (-1.14, 0.96)	-0.25 (-1.34, 0.83)
Education	NVQ4/NVQ5/degree or equivalent	3604	Ref	Ref	3423	Ref	Ref
	Below degree		0.86 (-0.56, 2.27)	0.82 (-0.55, 2.18)		0.43 (-0.49, 1.34)	0.38 (-0.51, 1.27)
	No qualification		-0.45 (-2.15, 1.25)	0.91 (-0.88, 2.71)		-0.68 (-1.62, 0.25)	-0.33 (-1.29, 0.62)
Employment	Professional	3414	Ref	Ref	3245	Ref	Ref
	Intermediate		-1.29 (-2.80, 0.21)	-0.46 (-1.86, 0.94)		-0.47 (-1.48, 0.54)	-0.16 (-1.17, 0.84)
	Routine and manual		-0.83 (-2.31, 0.65)	-0.57 (-1.96, 0.82)		-0.21 (-1.06, 0.64)	-0.10 (-0.92, 0.73)
Smoking	Current	3607	Ref	Ref	3425	Ref	Ref
	Ex-regular		-1.53 (-3.45, 0.39)	-0.65 (-2.43, 1.13)		-0.30 (-1.47, 0.88)	0.02 (-1.17, 1.20)
	Never		-1.57 (-3.53, 0.39)	-0.49 (-2.31, 1.33)		0.05 (-1.09, 1.19)	0.50 (-0.61, 1.61)

		ALT			AST		
		Weighted n	Univariate Coef (95%CI)	Age and sex adjusted Coef (95%CI)	Weighted n	Univariate OR (95%CI)	Age and sex adjusted OR (95%CI)
BMI	BMI continuous	3312	0.81 (0.66, 0.96)**	0.86 (0.70, 1.01)**	3144	0.20 (0.12, 0.29)**	0.21 (0.13, 0.29)**
	Normal	3262	Ref	Ref	3094	Ref	Ref
	Overweight		5.11 (3.97, 6.25)**	4.87 (3.76, 5.97)**		1.46 (0.68, 2.24)**	1.16 (0.36, 1.97)**
	Obese		10.67 (8.68, 12.66)**	11.17 (9.21, 13.13)**		2.94 (1.99, 3.88)**	2.98 (2.05, 3.91)**
Waist circumference	Male	1730	0.35 (0.27, 0.43)**	0.50 (0.40, 0.59)**	1631	0.03 (-0.02, 0.08)	0.08 (0.03, 0.13)**
	Female	1791	0.23 (0.17, 0.28)**	0.24 (0.18, 0.30)**	1708	0.08 (0.04, 0.11)**	0.07 (0.03, 0.11)**
Waist circumference (NICE categorisation)	Low (<94cm men, <80cm women)	3256	Ref	Ref	3090	Ref	Ref
	High (94-102 men, 80-88 women)		3.88 (2.40, 5.37)**	5.35 (3.93, 6.78)**		0.85 (-0.28, 1.98)	1.21 (0.12, 2.30)*
	Very high (>102 men, >88 women)		7.04 (5.40, 8.68)**	10.23 (8.44, 12.03)**		1.00 (0.01, 1.99)*	1.94 (1.00, 2.88)**
Central obesity	Male	1612	-12.39 (-17.27, -7.51)**	-10.99 (-15.72, -6.26)**	1519	-2.88 (-6.20, 0.44)	-2.15 (-5.51, 1.22)
	Female	1644	-3.77 (-6.21, -1.34)**	-4.05 (-6.48, -1.63)**	1571	-1.13 (-2.77, 0.51)	-0.06 (-0.10, -0.03)**
Diabetes	No diabetes	3555	Ref	Ref	3387	Ref	Ref
	Doctor diagnosed		2.70 (0.28, 5.12)*	3.40 (0.89, 5.92)**		0.07 (-1.69, 1.84)	0.11 (-1.75, 1.96)
	undiagnosed		9.93 (4.50, 15.36)**	10.81 (5.70, 15.91)**		4.52 (1.34, 7.70)**	4.57 (1.44, 7.71)**
Alcohol	Total units/week	3577	0.07 (0.04, 0.10)**	0.04 (0.01, 0.07)**	3396	0.05 (0.03, 0.07)**	0.04 (0.02, 0.06)**
Alcohol	None	3577	Ref	Ref	3396	Ref	Ref
	Low		-0.44 (-2.24, 1.36)	-0.93 (-2.65, 0.79)		0.09 (-0.91, 1.10)	-0.12 (-1.10, 0.86)
	Intermediate		2.23 (0.00, 4.45)	0.23 (-1.87, 2.33)		1.62 (0.28, 2.95)*	0.80 (-0.49, 2.08)
	High		3.78 (1.17, 6.39)**	2.57 (0.07, 5.08)*		4.15 (2.19, 6.11)**	3.60 (1.70, 5.50)**
Physical activity MVPA	Inactive	3573	Ref	Ref	3392	Ref	Ref
	Low or some activity		0.12 (-2.44, 2.67)	-0.11 (-2.49, 2.27)		-0.28 (-1.59, 1.03)	-0.33 (-1.61, 0.95)
	Meets MVPA guidelines		0.82 (-0.78, 2.43)	-0.67 (-2.30, 0.95)		1.16 (0.13, 2.18)	0.64 (-0.38, 1.67)
* Denotes significance at the 0.05 level ** denotes significance at the 0.01 level							

B.3 Linear regression model for FIB-4 and APRI

Table 39: Univariate and age/sex adjusted linear regression model for FIB-4 and APRI

		FIB-4			APRI		
		Weighted n	Univariate OR (95%CI)	Age and sex adjusted OR (95%CI)	Weighted n	Univariate OR (95%CI)	Age and sex adjusted OR (95%CI)
Age	Age, years	3388	0.02 (0.02, 0.03)**	0.02 (0.02, 0.03)**	3389	0.00 (-0.00, 0.00)	0.00 (0.00, 0.00)*
Sex	Male	3388	Ref	Ref	3389	Ref	Ref
	Female		-0.08 (-0.13, -0.04)**	-0.11 (-0.14, -0.07)**		-0.07 (-0.08, -0.06)**	-0.07 (-0.08, -0.06)**
Ethnicity	White	3382	Ref	Ref	3383	Ref	Ref
	Black		-0.09 (-0.25, 0.07)	0.05 (-0.04, 0.15)		0.00 (-0.03, 0.03)	0.01 (-0.02, 0.03)
	Asian		-0.29 (-0.38, -0.21)**	-0.04 (-0.09, 0.01)		-0.01 (-0.03, 0.01)	-0.01 (-0.03, 0.02)
	Mixed/multiple/Other		-0.25 (-0.37, -0.12)**	0.04 (-0.03, 0.11)		0.02 (-0.01, 0.05)	0.02 (-0.01, 0.05)
Index of multiple deprivation	Least deprived	3388	Ref	Ref	3389	Ref	Ref
	2nd		-0.12 (-0.20, -0.04)**	-0.04 (-0.09, 0.01)		0.01 (-0.01, 0.03)	0.01 (-0.01, 0.02)
	3rd		-0.16 (-0.25, -0.07)**	-0.03 (-0.09, 0.03)		0.00 (-0.02, 0.02)	-0.00 (-0.02, 0.02)
	4th		-0.19 (-0.28, -0.10)**	-0.00 (-0.06, 0.06)		0.01 (-0.01, 0.03)	0.01 (-0.01, 0.03)
	Most deprived		-0.28 (-0.36, -0.20)**	-0.06 (-0.10, -0.01)		-0.01 (-0.02, 0.00)	-0.01 (-0.02, 0.01)
Education	NVQ4/NVQ5/degree or equivalent	3385	Ref	Ref	3386	Ref	Ref
	Below degree		0.05 (-0.00, 0.11)	0.01 (-0.02, 0.04)		0.01 (-0.00, 0.02)	0.01 (-0.01, 0.02)
	No qualification		0.42 (0.34, 0.50)**	-0.02 (-0.07, 0.04)		0.00 (-0.01, 0.02)	-0.00 (-0.02, 0.01)
Employment	Professional	3207	Ref	Ref	3208	Ref	Ref
	Intermediate		0.05 (-0.01, 0.12)	0.01 (-0.03, 0.05)		-0.01 (-0.02, 0.01)	-0.00 (-0.01, 0.01)
	Routine and manual		-0.01 (-0.07, 0.04)	-0.01 (-0.04, 0.03)		-0.00 (-0.02, 0.01)	0.00 (-0.01, 0.01)
Smoking	Current	3388	Ref	Ref	3389	Ref	Ref
	Ex-regular		0.33 (0.26, 0.41)**	0.04 (-0.01, 0.09)		0.00 (-0.02, 0.02)	-0.00 (-0.02, 0.02)
	Never		0.13 (0.07, 0.20)**	0.06 (0.02, 0.10)**		0.00 (-0.01, 0.02)	0.01 (-0.01, 0.03)

		FIB-4			APRI		
		Weighted n	Univariate OR (95%CI)	Age and sex adjusted OR (95%CI)	Weighted n	Univariate OR (95%CI)	Age and sex adjusted OR (95%CI)
BMI	BMI continuous	3111	0.00 (0.00, 0.01)*	-0.01 (-0.01, -0.01)**	3111	0.00 (0.00, 0.00)**	0.00 (0.00, 0.00)*
	Normal	3064	Ref	Ref	3064	Ref	Ref
	Overweight		0.13 (0.07, 0.19)**	-0.07 (-0.11, -0.04)**		0.02 (0.01, 0.03)**	0.01 (-0.00, 0.02)
	Obese		0.09 (0.02, 0.15)**	-0.11 (-0.15, -0.07)**		0.02 (0.01, 0.04)**	0.02 (0.00, 0.03)**
Waist circumference	Male	1615	0.01 (0.01, 0.01)**	-0.01 (-0.01, -0.00)**	1615	0.00 (-0.00, 0.00)	0.00 (-0.00, 0.00)
	Female	1688	0.01 (0.00, 0.01)**	-0.00 (-0.01, -0.00)**	1688	0.00 (0.00, 0.00)**	0.00 (-0.00, 0.00)
Waist circumference (NICE categorisation)	Low (<94cm men, <80cm women)	3056	Ref	Ref	3056	Ref	Ref
	High (94-102 men, 80-88 women)		0.18 (0.12, 0.24)**	-0.07 (-0.11, -0.04)**		0.01 (-0.01, 0.02)	0.01 (-0.01, 0.02)
	Very high (>102 men, >88 women)		0.21 (0.15, 0.26)**	-0.14 (-0.18, -0.11)**		0.00 (-0.01, 0.02)	0.01 (-0.00, 0.02)
Central obesity	Male	1504	0.40 (0.27, 0.54)	0.10 (0.02, 0.18)*	1504	-0.01 (-0.05, 0.03)	-0.01 (-0.05, 0.03)
	Female	1552	0.25 (0.15, 0.36)**	0.08 (0.02, 0.14)*	1552	0.01 (-0.01, 0.03)	0.00 (-0.02, 0.02)
Diabetes	No diabetes	3369	Ref	Ref	3370	Ref	Ref
	Doctor diagnosed		0.36 (0.23, 0.48)**	-0.04 (-0.15, 0.06)		0.02 (-0.01, 0.05)	0.01 (-0.02, 0.04)
	undiagnosed		0.42 (0.26, 0.58)**	-0.05 (-0.20, 0.09)		0.07 (-0.00, 0.15)	0.06 (-0.01, 0.14)
Alcohol	Total units/week	3358	0.00 (0.00, 0.00)*	0.00 (0.00, 0.00)*	3359	0.00 (0.00, 0.00)**	0.00 (0.00, 0.00)**
Alcohol	None	3358	Ref	Ref	3359	Ref	Ref
	Low		-0.04 (-0.11, 0.04)	0.00 (-0.04, 0.05)		-0.00 (-0.02, 0.01)	-0.01 (-0.02, 0.01)
	Intermediate		0.02 (-0.07, 0.11)	-0.01 (-0.06, 0.05)		0.02 (-0.00, 0.03)	-0.00 (-0.02, 0.02)
	High		0.16 (-0.03, 0.35)	0.12 (-0.02, 0.27)		0.07 (0.03, 0.11)	0.05 (0.01, 0.09)
Physical activity MVPA	Inactive	3355	Ref	Ref	3356	Ref	Ref
	Low or some activity		-0.17 (-0.26, -0.08)**	-0.00 (-0.06, 0.05)		-0.00 (-0.03, 0.02)	-0.00 (-0.02, 0.02)
	Meets MVPA guidelines		-0.23 (-0.31, -0.15)**	0.03 (-0.02, 0.08)		0.01 (-0.01, 0.02)	0.0 -0.01, 0.02)
* Denotes significance at the 0.05 level ** denotes significance at the 0.01 level							

Appendix C

C.1 Alcohol related interview questions used in the National Diet and Nutrition Survey (NDNS)

C.1.1 Self-completion booklet offered for young adults aged 18-24 years

SELF-COMPLETIONS
FOR RESPONDENTS AGED 8-24

IF (Age = 18-24) THEN
DrinIntr
INTERVIEWER: SMOKING AND DRINKING SELF-COMPLETION BOOKLET.
The next set of questions are about smoking cigarettes and drinking alcohol. We can either continue using the laptop to answer the questions, or you can fill in your answers in this booklet. Which would you prefer to do?
IS THE YOUNG PERSON TO CONTINUE WITH QUESTIONS IN CAPI OR ARE THEY TO BE GIVEN A BOOKLET (PEACH COVER)?
1 Asked "Continue with questions in CAPI"
2 Given "Given self completion booklet"

IF (Age = 11-24) THEN
SCIntro
INTERVIEWER: Prepare self completion booklet for ages (8-12: GREEN cover) / (13-15: PALE BLUE cover) / (16-24: PEACH cover) by entering serial numbers.
Check that you have the correct person number.
Name·····Point··Address··Check letter··Person number
1 Continue

IF (Age = 8-10) THEN
SCIntCh
Here is a little booklet which I would like to ask (child's name) to complete for him/herself. It asks children if they have ever tried cigarettes or alcohol. May I explain it to you/him/her?
INTERVIEWER: If asked, show GREEN booklet to (child's name).
If agrees, prepare GREEN booklet.
Name·····Point··Address··Check letter··Person number
INTERVIEWER: Explain to child how to complete and show example in booklet.
1 Continue

SComp2
I would now like you to answer some questions by completing this booklet on your own. The questions cover smoking and drinking.
INTERVIEWER: Explain how to complete booklet and show example in booklet.
1 Continue

IntDemog
INTERVIEWER: Wait until (respondent's name) has completed the self-completion booklet, then thank them for completing it and ask them to return it to you.
1 Continue

DRINKING

EVERYONE PLEASE ANSWER

DDRINK

Q11 Do you ever drink alcohol nowadays, including drinks you brew or make at home?

Tick one box

1075

Yes [1] → **Go to question 14**

No [2] → **Go to question 12**

DDRINKAN

Q12 Just to check, does that mean you never have an alcoholic drink nowadays, or do you have an alcoholic drink very occasionally, perhaps for medicinal purposes or on special occasions like Christmas and New Year?

Tick one box

1076

Very occasionally [1] → **Go to question 14**

Never [2] → **Go to question 13**

DALWAYTT

Q13 Have you always been a non-drinker or did you stop drinking for some reason?

Tick one box

1077

Always a non-drinker [1]

Used to drink but stopped [2]

→ **END**

DDRINKAG

Q14 How old were you the first time you ever had a proper alcoholic drink?

1078 - 1079

Write in how old you were then [ ] → **Go to question 15**

DDRINKOF

Q15 Thinking now about all kinds of drinks, how often have you had an alcoholic drink of any kind during the last 12 months?

Tick one box

1050-1051

Almost every day	01	
Five or six days a week	02	
Three or four days a week	03	
Once or twice a week	04	
Once or twice a month	05	→ **Go to question 16**
Once every couple of months	06	
Once or twice a year	07	
Not at all in the last 12 months	08	→ **END**

DDRINKL7

Q16 Did you have an alcoholic drink in the seven days ending yesterday?

Tick one box

1052

Yes	1	→ **Go to question 17**
No	2	→ **END**

DDRNKDAY

Q17 On how many days out of the last seven did you have an alcoholic drink?

Tick one box

1053

One	1	
Two	2	
Three	3	
Four	4	→ **Go to question 18**
Five	5	
Six	6	
Seven	7	

Q18 Please think about the day in the last week on which you drank the most. (If you drank the same amount on more than one day, please answer about the most recent of those days.)

From this list, please tick all the types of alcoholic drink which you drank on that day. For the ones you drank, write in how much you drank on that day. EXCLUDE NON-ALCOHOL OR LOW-ALCOHOL DRINKS, EXCEPT SHANDY.

DDKTYP01-07

TICK ALL DRINKS DRUNK ON THAT DAY		WRITE IN HOW MUCH DRUNK ON THAT DAY				
	1084-1099	Glasses (count doubles as 2 singles)	Pints	Large cans or bottles	Small cans or bottles	
Normal strength beer, lager, stout, cider or shandy (less than 6% alcohol)-exclude bottles/cans of shandy.	01		*NBERQPT7*	*DNBL7Q2*	*DNBL7Q3*	1100-1107
Strong beer, lager, stout or cider (6% alcohol or more, such as Tennants Super, Special Brew, Diamond White)	02		*SBERQPT7*	*DSBL7Q2*	*DSBL7Q3*	1108-1115
Spirits or liqueurs, such as gin, whisky, rum, brandy, vodka, or cocktails	03	*DSPIRL7Q*				1116-1117
Sherry or martini (including port, vermouth, cinzano, dubonnet)	04	*DSHRL7Q*				1118-1119
		Large glasses (250ml)	Standard glasses (175ml)	Small glasses (125ml)	Bottles (750ml)	
Wine (including babycham and champagne). You can write in parts of a bottle e.g. half a bottle	05	*DW250ML*	*DW175ML*	*DW125ML*	*DWBTL*	1120-1128
Alcoholic soft drink ('alcopop') such as Hooch, or a pre-mixed alcoholic drink such as Bacardi Breezer, WKD or Smirnoff Ice	06				Small cans or bottles *DPOPSL7Q*	1129-1130
Other kinds of alcoholic drink **WRITE IN NAME OF DRINK**		Glasses (count doubles as 2 singles)	Pints	Large cans or bottles	Small cans or bottles	
1.	07					1131-1140
2.	08					1141-1150

Spare 1151 - 1170

Thank you for answering these questions.

Please give the booklet back to the interviewer.

C.1.2 Interview questions for resondents aged 18 years and over

DRINKING
FOR RESPONDENTS AGED 18 AND OVER

IF (no self completion AND Age = 16-24) OR (AgeP = 25+) THEN
Drink
I am now going to ask you a few questions about what you drink - that is if you drink.
Do you ever drink alcohol nowadays, including drinks you brew or make at home?
1 Yes
2 No

IF (Drink = No) THEN
DrinkAny
Could I just check, does that mean you never have an alcoholic drink nowadays, or do you have an alcoholic drink very occasionally, perhaps for medicinal purposes or on special occasions like Christmas and New Year?
1 Occ "Very occasionally"
2 Never "Never"

IF (DrinkAny = Never) THEN
AlwaysTT
Have you always been a non-drinker or did you stop drinking for some reason?
1 Alwys "Always a non-drinker"
2 Stopped "Used to drink but stopped"

IF (Drink = Yes) OR (DrinkAny = Occ) THEN
DrinAge
How old were you the first time you ever had a proper alcoholic drink?
: 3..97

IF (Drink = Yes) OR (DrinkAny = Occ) THEN
DrinkOft
SHOW CARD W
Thinking now about all kinds of drinks, how often have you had an alcoholic drink of any kind during the last 12 months?
1 AED "Almost every day"
2 Five "Five or six days a week"
3 Three "Three or four days a week"
4 OneWk "Once or twice a week"
5 OneMth "Once or twice a month"
6 CupMth "Once every couple of months"
7 OneYr "Once or twice a year"
8 NotYr "Not at all in the last 12 months"

IF (DrinkOft AED....OneYr) THEN
DrinkL7
Did you have an alcoholic drink in the last seven days, that is since (date 7 days ago) until yesterday?
1 Yes
2 No

IF (DrinkL7 = Yes) THEN
DrnkDay
On how many days out of the last seven did you have an alcoholic drink?
: 1..7

IF (DrnkDay = 2...7) THEN
DrnkSame
Did you drink more on one of the days/some days than others, or did you drink about the same on both/each of those?

1	Varied	"Drank more on one/some day(s) than other(s)"
2	Same	"Same each day"

IF (DrinkL7 = Yes) THEN
WhichDay
Which day (last week) did you last have an alcoholic drink (have the **most** to drink)?

1	Sunday	"Sunday"
2	Monday	"Monday"
3	Tuesday	"Tuesday"
4	Wednesday	"Wednesday"
5	Thursday	"Thursday"
6	Friday	"Friday"
7	Saturday	"Saturday"

IF (DrinkL7 = Yes) THEN
DrnkType
SHOW CARD X
Thinking about last (day from WhichDay), what types of drink did you have that day?
CODE ALL THAT APPLY.

1	NBeer	"Normal strength beer/lager/cider/shandy"
2	SBeer	"Strong beer/lager/cider"
3	Spirits	"Spirits or liqueurs"
4	Sherry	"Sherry or martini"
5	Wine	"Wine"
6	Pops	"Alcopops/pre-mixed alcoholic drink"
7	Other	"Other alcoholic drinks"
8	Low	"Low alcohol drinks only"

IF (DrnkType = NBeer) THEN
NBrL7
Still thinking about last (day from WhichDay), how much **normal strength beer, lager, stout, cider or shandy** (excluding cans and bottles of shandy) did you drink that day?
INTERVIEWER: Code measures that you are going to use.

1	HPints	"Half pints"
2	SmCans	"Small cans"
3	LgCans	"Large cans"
4	Bottles	"Bottles"

IF (DrnkType = NBeer) THEN
NBrL7Q
ASK OR CODE: How many (answer from NBrL7) of **normal strength beer, lager, stout, cider or shandy** (excluding cans and bottles of shandy) did you drink that day?
: ARRAY [1..4] OF 1..97

IF (DrnkType = NBeer) THEN
NBotL7
ASK OR CODE: What make of **normal strength beer, lager, stout or cider** did you drink from bottles on that day?
INTERVIEWER: If respondent drank different makes code which they drank most.
: STRING [21]

IF (DrnkType = SBeer) THEN
SBrL7
Still thinking about last (day from WhichDay), how much **strong beer, lager, stout or cider** did you drink that day?
INTERVIEWER: Code measures that you are going to use.

1	HPints	"Half pints"
2	SmCans	"Small cans"
3	LgCans	"Large cans"
4	Bottles	"Bottles"

IF (DrnkType = SBeer) THEN
SBotL7
ASK OR CODE: What make of **strong beer, lager, stout or cider** did you drink from bottles on that day?
INTERVIEWER: If respondent drank different makes code which they drank most.
: STRING [21]

IF (DrnkType = Spirits) THEN
SpirL7
Still thinking about last (day from WhichDay), how much spirits or liqueurs (such as gin, whisky, brandy, rum, vodka, advocaat or cocktails) did you drink on that day?
INTERVIEWER: Code the number of singles - count doubles as two singles.
: 1..97

IF (DrnkType = Sherry) THEN
ShryL7
Still thinking about last (day from WhichDay), how much sherry or martini, including port, vermouth, Cinzano and Dubonnet did you drink on that day?
INTERVIEWER: Code the number of glasses.
: 1..97

IF (DrnkType = Wine) THEN
WineL7
Still thinking about last (day from WhichDay), how much wine, including Babycham and champagne, did you drink on that day?
INTERVIEWER Code the measure the respondent used.
Please note that respondent may give answer in bottles and glasses.
Please code the relevant option.

1	Bottle	"Bottle or parts of bottle"
2	Glasses	"Glasses"
3	Both	"Both bottles or parts of bottle, and glasses"

IF (DrnkType = Wine) THEN
WL7Bt
INTERVIEWER: Code the number of 125ml glasses drunk **from the bottle** by the respondent.
E.g. If they drank half a bottle, code 3 glasses.

1 bottl	=	6 glasses.

1/2 bottle = 3 glasses.
1/3 bottle = 2 glasses.
1/4 bottle = 1.5 glasses.
1 litre = 8 glasses.
1/2 litre = 4 glasses.
1/3 litre = 2.5 glasses.
1/4 litre = 2 glasses.
If respondent has answered in bottles or litres, convert to glasses using the information provided on the screen.
For example, if a respondent said they shared a bottle with one other person and they shared it equally, code 3 glasses.
: 1.0..97.9

IF (DrnkType = Wine) THEN
WL7Gl
INTERVIEWER: Code the number of glasses (**drunk as glasses**).
: 1.0..97.9

IF (DrnkType = Wine) THEN
WL7Glz
Were you drinking from a large, standard, or small glass?
INTERVIEWER: If respondent drank from two or three different size glasses, please code all that apply.
Please note that if respondent was drinking in a pub or wine bar and had a small glass, this would usually be 175ml.

1	Large	"Large glass (250ml)"
2	Standard	"Standard glass (175ml)"
3	Small	"Small glass (125ml)"

IF (WL7Glz=1) THEN
Ml250Glz
How many large glasses (250ml) did you drink?
: 1.0..97.9

IF (WL7Glz=2) THEN
Ml175Glz
How many standard glasses (175ml) did you drink?
: 1.0..97.9

IF(WL7Glz=3) THEN
Ml125Glz
How many small glasses (125ml) did you drink?
: 1.0..97.9

IF (DrnkType = Pops) THEN
PopsL7
Still thinking about last (day from WhichDay), how much **alcoholic soft drink** ('alcopop') did you drink on that day?
INTERVIEWER: Code measures that you are going to use.

1	SmCans	"Small cans"
2	Bottles	"Bottles"

IF (DrnkType = Pops) THEN
PopsL7Q

ASK OR CODE: How many (answer from PopsL7) of **alcoholic soft drink** ('alcopop') did you drink on that day?
: ARRAY [1..2] OF 1..97

IF (DrnkType = other) THEN
OthL7TA
Still thinking about last (day from WhichDay), what other type of alcoholic drink did you drink on that day?
INTERVIEWER: Code first mentioned only.
: STRING [30]

IF (DrnkType = other) THEN
OthL7QA
How much (answer from OthL7TA) did you drink on that day?
INTERVIEWER: Write in how much. Remember to specify half pints/ singles/ glasses/ bottles.
: STRING [30]

IF (DrnkType = other) THEN
OthL7B
Did you drink any other type of alcoholic drink on that day?
1 Yes
2 No

IF (DrnkType = other) THEN
OthL7TB
Still thinking about last (day from WhichDay), what other type of alcoholic drink did you drink on that day?
INTERVIEWER: Code first mentioned only.
: STRING [30]

IF (DrnkType = other) THEN
OthL7QB
How much (answer from OthL7TB) did you drink on that day?
INTERVIEWER: Write in how much. Remember to specify half pints/ singles/ glasses/ bottles.
: STRING [30]

IF (DrnkType = other) THEN
OthL7C
Did you drink any other type of alcoholic drink on that day?
1 Yes
2 No

IF (DrnkType = other) THEN
OthL7TC
Still thinking about last (day from WhichDay), what other type of alcoholic drink did you drink on that day?
INTERVIEWER: Code first mentioned only.
: STRING [30]

IF (DrnkType = other) THEN
OthL7QC
How much (answer from OthL7TC) did you drink on that day?

INTERVIEWER: Write in how much. Remember to specify half pints/ singles/ glasses/ bottles.
: STRING [30]

IF (current age is 5 or more years greater than age first had alcoholic drink) THEN DrAmount

Compared to five years ago, would you say that on the whole you drink more, about the same or less nowadays?

1	More	"More nowadays"
2	Same	"About the same"
3	Less	"Less nowadays"

CARD W

1	Almost every day
2	Five or six days a week
3	Three or four days a week
4	Once or twice a week
5	Once or twice a month
6	Once every couple of months
7	Once or twice a year
8	Not at all in the last 12 months

CARD X

1	Normal strength beer / lager / cider / shandy
2	Strong beer / lager / cider
3	Spirits or liqueurs
4	Sherry or martini
5	Wine
6	Alcopops / pre-mixed alcoholic drink
7	Other alcoholic drinks
8	Low alcohol drinks only

C.2 Food and drink diary: example page from instructions

Time	Where? With Whom? TV on? At table?	Food/Drink description & preparation	Brand Name	Portion size or quantity eaten
		5pm to 8pm		
6.30 pm	Pub Partner TV on At table	Gin Tonic water diet Lager 3.8% alcohol Salted peanuts	Gordon's Schweppes Draught, Carlsberg KP	Single measure 1/2 small glass 1 pint 1 handful
8 pm	Dining room Family No TV At table	Spaghetti, wholemeal Bolognese sauce (see recipe) Courgettes (fried in butter) Tinned peaches in juice (juice drained) Single cream UHT Orange squash No Added Sugar	Tesco's own Prince's Sainsbury's own cream Sainsbury's own	3b 6 tablespoons 4 tablespoons 3 halves 1 tablespoon 200ml glass, 1 part squash, 3 parts tap water
		8pm to 10pm		
9 pm	Sitting room Alone TV on Not at table	Grapes, green, seedless Chocolates, chocolate creams Potato crisps, Prawn Cocktail	 Bendicks Walkers	15 2 25g bag (from multipack)
		10pm to 6am		
10.30 pm	Bed room Partner No TV Not at table	Camomile tea (no milk or sugar)	Twinings	1 mug

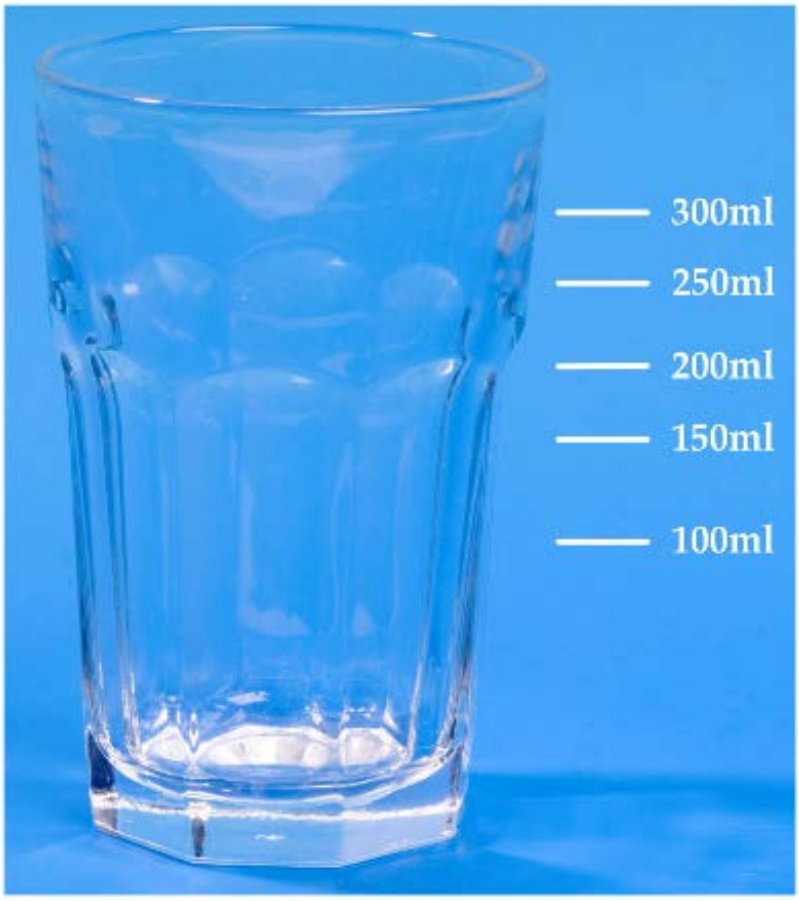
C.3 Food and drink diary: information given about glass sizes

Typical quantities of drinks in various containers measured in millilitres (ml)

	Small glass	Average glass	Large glass	Vending cup	Cup	Mug
Soft drinks	150	200	300			
Wine	125	175	250			
Hot drinks				170	190	260

Glasses come in different shapes and sizes. On the next page is a life size glass showing approximate volumes. You can use this picture as a guide for estimating how much volume of drink the glass you are drinking from holds.

Life Size Glass



C.5 Sociodemographic characteristics of sample by reported binge drinking and alcohol consumption frequency

Table 40: Sociodemographic characteristics of sample, by binge drinking status (binge drinking defined as yes if participant reported drinking more than 6 units on the heaviest drinking day for women, more than 8 units for men)

		Binge drinking	No binge drinking	Chi squared P value
Age in years (n=4214)	18-24 25-49 50-64 65+	17.2% 53.7% 21.9% 7.1%	7.8% 40.4% 27.2% 24.7%	P<0.001**
Sex (n=4214)	Male Female	62.0% 38.0%	50.2% 49.8%	P<0.001**
Ethnicity (n=4211)	White Other	96.8% 3.2%	93.5% 6.5%	P=0.001**
Education (n=4009)	Finished at 16yrs or under Finished at 17 or 18yrs Finished at 19yrs or over	43.9% 25.0% 31.2%	43.7% 22.9% 33.4%	P=0.421
Employment ǂ (n=3612)	NS-SEC class 1 NS-SEC class 2 NS-SEC class 3	54.4% 10.8% 34.8%	58.6% 9.7% 31.7%	P=0.197
Cigarette smoking status (n=4213)	Current smoker Ex regular smoker Never regular smoker	27.6% 24.4% 48.1%	17.5% 27.6% 54.9%	P<0.001**
Time spent at moderate or vigorous physical activity median (95% CI) (n=2410)		0.72	0.71	p=0.195

* denotes significance at the 0.05 level ** denotes significance at the 0.01 level

ǂ National Statistics Socioeconomic Classification class 1 = higher managerial, administrative and professional occupations, class 2 = intermediate occupations, class 3 = routine and manual occupations[133]

Table 41: Sociodemographic characteristics of sample by frequency of reported alcohol consumption in last 12 months

Variable categories		Above UK limits	Within UK limits	Infrequent	Not at all	Chi squared p value
		% of alcohol consumption category within variable categories – weighted proportion				
Whole sample (n=6.590)		13.5%	44.7%	32.5%	9.3%	
Age in years (n=6590)	mean (SE)	57.5 (0.67)	45.6 (0.44)	46.2 (0.54)	48.3 (1.20)	
	18-24	2.2%	11.9%	14.4%	10.4%	<0.001**
	25-49	28.7%	48.2%	44.4%	49.2%	
	50-64	34.1%	24.1%	20.5%	15.8%	
	65+	35.1%	15.7%	20.8%	24.6%	
Sex (n=6597)	Male	60.8%	54.0%	39.4%	38.4%	<0.001**
	Female	39.2%	46.0%	60.6%	61.6%	
Ethnicity (n=6591)	White	96.9%	94.4%	89.4%	46.8%	<0.001**
	Mixed ethnicity	0.1%	1.0%	2.1%	0.7%	
	Black	1.2%	1.8%	3.2%	9.9%	
	Asian	0.3%	2.0%	3.5%	35.3%	
	Other	1.4%	0.8%	1.8%	7.3%	
Education (n=6237)	Finished at 16yrs or under	52.6%	41.3%	49.6%	44.0%	<0.001**
	Finished at 17 or 18yrs	18.3%	23.9%	24.2%	17.5%	
	Finished at 19yrs or over	29.1%	34.8%	26.3%	38.6%	
Employment ł (n=6471)	NS-SEC class 1	63.9%	56.3%	42.9%	37.0%	<0.001**
	NS-SEC class 2	9.1%	10.2%	11.5%	11.5%	
	NS-SEC class 3	27.0%	33.6%	45.7%	51.5%	
Cigarette smoking status (n=6589)	Current smoker	23.1%	19.5%	22.6%	10.3%	<0.001**
	Ex regular smoker	37.6%	23.7%	20.7%	12.2%	
	Never regular smoker	39.3%	56.8%	56.7%	77.5%	
Time spent at moderate or vigorous physical activity median (95%CI) (n=3666)		0.74 (0.64, 0.86)	0.74 (0.69, 0.82)	0.53 (0.50, 0.59)	0.32 (0.20, 0.40)	

ł National Statistics Socioeconomic Classification class 1 = higher managerial, administrative and professional occupations, class 2 = intermediate occupations, class 3 = routine and manual occupations[133]

* denotes significance at the 0.05 level ** denotes significance at the 0.01 level

Glossary of Terms

Absolute risk The risk that a future outcome (disease, death) will occur over a specified period of time.

AUDIT Score An alcohol screening tool questionnaire. AUDIT-C refers to a short, 3 question tool. A high score in AUDIT-C prompts use of the full AUDIT screening tool.

Body mass index Height in square metres, divided by weight in kilograms. Expressed as kg/m^2.

Cirrhosis Scarring of the liver, caused by long-term liver damage, which leads to loss of liver function.

Confidence interval The range of values either side of an estimated value in a sample, within which the true value in the population may lie. There is a 95% chance that the true population value lies within the range of the 95% confidence interval for an estimate.

False positive A test result which indicates that a person has a certain disease, when the true situation is that the person does not have the disease.

False negative A test result which indicates that a person does not have a certain disease, when the true situation is that the person does have the disease.

Hepatocellular carcinoma The most common type of liver cancer, often secondary to cirrhosis.

High cut-off The use of a cut-off for staging of liver fibrosis by a non-invasive fibrosis marker that aims to maximise specificity. A result above the cut-off suggests disease.

Liver biopsy Removal of a small sample of liver tissue, using a hollow needle, for histopathological examination.

Liver fibrosis Formation of excessive fibrous tissue in the liver.

Low cut-off The use of a cut-off for staging of liver fibrosis by a non-invasive fibrosis marker that aims to maximise sensitivity. A result below the cut-off suggests no disease.

Meta-analysis Statistical techniques used to combine the results of two or more studies and obtain a combined estimate of effect.

Negative predictive value The proportion of true negative results, out of all negative results.

Non-alcoholic fatty liver disease Liver disease characterised by the accumulation of fat in the liver. Usually the definition is limited to people who do not drink alcohol above a specified limit.

Non-alcoholic steatohepatitis The progressive form of non-alcoholic fatty liver disease. Inflammation may lead to fibrosis and cirrhosis.

Obese Body mass index ≥30 kg/m^2.

Overweight Body mass index ≥25 but <30 kg/m^2.

Positive predictive value The proportion of true positive results, out of all positive results.

Reference standard Established test against which the accuracy of a new test for detecting a particular condition can be evaluated.

Relative risk The number of times more or less likely an event is to happen in one group compared with another.

Sensitivity The ability of a test to correctly identify as having disease, all those who actually have the disease.

Sensitivity analysis A further analysis to give an indication of the uncertainty in, or robustness of, the results of the main analysis.

Specificity The ability of a test to correctly identify as not having disease, all those who do not have the disease.

Spectrum bias Potential error in the interpretation of the performance of a diagnostic test, due to different patient mix in different settings.

Steatosis A condition characterised by the accumulation of excess fat within the liver.

True negative A person without the disease correctly identified as negative by the index test.

True positive A person with the disease correctly identified as positive by the index test.

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