Obesity and type 2 diabetes are important risk factors underlying previously undiagnosed cirrhosis in general practice: a cross-sectional study using Transient Elastography

David J Harman[1], **Stephen D Ryder[1]**, **Martin W James[1]**, **Emilie A Wilkes[1]**, **Timothy R Card[1,2]**, **Guruprasad P Aithal[1,3]*, Indra Neil Guha[1,3]*** *=joint senior authors

[1] National Institute for Health Research (NIHR) Nottingham Biomedical Research Centre (BRC), Nottingham University Hospitals NHS Trust and University Of Nottingham, Nottingham, NG7 2UH, United Kingdom[1]
(DJ Harman – Clinical Research Fellow in Hepatology; SD Ryder, MW James, EA Wilkes – Consultant Hepatobiliary Physician; TR Card - Clinical Associate Professor of GI epidemiology and Consultant Gastroenterologist; GP Aithal – Professor of Hepatology and Consultant Hepatobiliary Physician; IN Guha - Clinical Associate Professor of Hepatology and Consultant Hepatobiliary Physician)

[2]Division of Epidemiology and Public Health, Clinical Sciences Building Phase 2, City Hospital Campus, University of Nottingham, Nottingham, NG5 1PB, United Kingdom[2]

[3]Nottingham Digestive Diseases Centre, University of Nottingham

Corresponding Author:
Dr Neil Guha
NIHR Nottingham Biomedical Research Centre
E Floor, West Block
Queens Medical Centre,
Derby Road,
Nottingham
NG7 2UH
Email: neil.guha@nottingham.ac.uk
Telephone: 01159249924 ext 70609

Short Title: Undiagnosed cirrhosis in general practice

Manuscript Word Count (incl. References): 5,751 words
Abstract Word Count: 250 words
Tables: 5
Figures: 2

Abbreviations (in order of appearance):

ALD, alcoholic liver disease; NAFLD, non-alcoholic fatty liver disease; TE, transient elastography; BMI, body mass index; kPa, kilopascals; HDL, high density lipoprotein; ALT, alanine aminotransferase; OR, odds ratio; T2DM, type 2 diabetes mellitus; CLD, chronic liver disease; NASH, non-alcoholic steatohepatitis; PHG, portal hypertensive gastropathy; LSM, liver stiffness measurement

Keywords:
Alcohol-related liver disease, cirrhosis, liver fibrosis, liver function tests, non-alcoholic fatty liver disease

Abstract

Background:
Rising cirrhosis incidence and mortality in the United Kingdom has been attributed predominantly to excess alcohol consumption. However, metabolic risk factors such as type 2 diabetes and obesity may also be important.

Aim:
To screen at-risk individuals in general practice for undetected cirrhosis using transient elastography and study the risk factors underlying these cases.

Methods:
The study was undertaken in 4 general practices (adult patient population 20,868) between February 2012 and September 2014. Patients with defined risk factors for chronic liver disease (hazardous alcohol use and/or type 2 diabetes) were identified from the General Practice electronic records and invited for transient elastography. Elevated liver stiffness was defined as ≥8 kilopascals. Cirrhosis was confirmed by established histological, radiological and biochemical methods.

Results:
2,368 patients were invited for transient elastography and 899/919 who attended (97.8%) had valid measurements. Of these 230 patients had elevated liver stiffness (25.6%) and 27 had cirrhosis (2.9%). Risk factors for new cirrhosis diagnoses were obesity and/or type 2 diabetes in 16 patients (59.3%), alcohol alone in 3 (11.1%) and both alcohol and obesity and/or diabetes in 8 (29.6%). Presence of cirrhosis was significantly increased in obese patients with type 2 diabetes or hazardous alcohol use compared to non-obese (odds ratio 9.4 (95% CI 2.2-40.9) and 5.6 (95% CI 1.6-19.7) respectively).

Conclusions:
The number of new cases of cirrhosis diagnosed clearly demonstrates that existing estimates of prevalence are likely to be gross underestimates. Obesity was an important risk factor for cirrhosis within both alcohol users and diabetics.

ClinicalTrials.gov registration: NCT02037867

Introduction:

Chronic liver disease continues to be a significant public health burden. In England, diagnosed cirrhosis incidence has increased by 50.6% between 1998 and 2009[1], and subsequently cirrhosis is now the third commonest cause of premature mortality in persons aged 20-54[2]. Population level alcohol consumption is still considered the major driver of liver-related mortality, and up to 62% of detected cirrhosis cases in the population are attributed to alcoholic liver disease (ALD)[1,3]. However, the rising population prevalence of metabolic syndrome risk factors means that non-alcoholic fatty liver disease (NAFLD) and related cirrhosis are becoming a more significant issue. Obesity prevalence in the United Kingdom has risen by 54% in men and 65% in women between 1993 and 2012, and the prevalence of type 2 diabetes is forecast to double between 2000 and 2030. Non-alcoholic fatty liver disease is therefore likely to become the leading cause of liver cirrhosis in the near future, and indeed in the USA NAFLD has already overtaken alcoholic liver disease as a cause of listing for liver transplantation[4]. Several studies have demonstrated the important synergism between body mass index and alcohol consumption, and the increased risk of progressive fibrosis[5], cirrhosis diagnoses[6] and liver-related death[7,8]. However, as NAFLD is discounted as a diagnosis in the presence of a specific cut-off of alcohol consumption (such as a weekly consumption of >14 units in women and >21 units in men), all cirrhosis in those with an alcohol consumption above the cut-off will be coded as alcohol related cirrhosis[9]. The overall impact of obesity, type 2 diabetes and other metabolic risk factors on cirrhosis incidence and liver-related outcomes is therefore likely to be greatly underestimated by current practice.

We have previously demonstrated that a community based service using transient elastography (TE) can detect appreciable quantities of previously unrecognised liver

disease among people with hazardous alcohol use and people with Type 2 diabetes[10]. We extended this study with additional recruitment, to study the association of alcohol and metabolic risk factors with chronic liver disease in a community setting. The aims of the current study are to characterise new clinically significant liver disease and cirrhosis within the screened population, and to identify the risk factors associated with elevated liver stiffness and cirrhosis.

Materials and Methods:

Study Setting

This was a cross-sectional study with recruitment from four general medical practices in Nottingham, United Kingdom. Of these, 2 primary care medical practices were located in an affluent suburban borough, whilst the remaining 2 practices were situated in predominantly deprived areas of the City of Nottingham District. The study period was 31 months from February 2012 to September 2014. All practices utilised the SystmOne general practice records system (TPP, United Kingdom) which facilitates live recording of clinical, anthropometric and biochemical patient data. Data is prospectively entered during all patients' primary care appointments with General Practitioners and Practice Nurses. The same database is used for patients' standard clinical care. Data is stored as searchable numeric data or prospectively coded with 'Read Codes' (clinical encoding of parameters including patient demographics, diagnoses, clinical signs and laboratory test results). The 'Read Codes' are based on electronic clinical management systems, in which the primary care clinician selects codes to record directly into the computerised medical record system. Local regulatory approval was obtained from the Leicester Research Ethics

Committee (study identification 13/EM/0123), and written informed consent was gained from patients.

Patient Selection

Patient selection for the current study has been previously published[10]. Briefly, adult patients (defined as aged 18 years or older) with selected risk factors for lifestyle related chronic liver disease were identified directly from the general medical practice electronic patient records. The electronic record search was performed at the commencement of the study. The studied risk factors were:

a) Hazardous alcohol use – this was defined as presence of any of i) >14 units per week ethanol consumption for women or >21 units per week ethanol consumption for men, ii) alcohol AUDIT questionnaire score ≥8[11] or iii) presence of Read codes related to hazardous, harmful or dependent alcohol consumption. Patients were not included as hazardous alcohol consumers if alcohol consumption data had not been recorded in the 5 years prior to study.

b) Type 2 Diabetes – Presence of Read codes related to a diagnosis of type 2 diabetes.

In addition, 3% of the study patients from the 4 studied practices were patients with persistently elevated serum alanine aminotransferase (ALT) levels (>35IU/L for women, >45IU/L for men), who had neither hazardous alcohol intake nor type 2 diabetes, and negative liver autoimmune and serological tests.

Patients were excluded from the study if i) there was definitive evidence of hepatic fibrosis or cirrhosis already identified from previous investigations, ii) there was a contraindication to transient elastography (pregnancy, indwelling cardiac device), iii) they had metastatic malignancy, iv) they were unable to consent to investigation due to significant cognitive impairment, or v) they were housebound and could not attend the community practice. In addition, patients who presented with symptoms of decompensated liver cirrhosis (e.g. jaundice, variceal bleeding, ascites) during the study period were excluded and instead triaged straight to urgent hospital-based care rather than being screened using TE in primary care.

Liver Stiffness Measurement

The methodology for invitation and screening of patients from the suburban medical practices has been published previously, and included an initial screening blood biomarker prior to transient elastography[10]. Patients from the inner city practices were invited directly for an appointment to undergo transient elastography. The scan was performed by one of three nurses, all of whom had received formal training in liver stiffness measurement and had previously performed more than two hundred liver stiffness acquisitions in the hospital setting. Our nurse led transient elastography service has been established since 2009 and we have published the evaluation of this service in 2012 showing only 5.3 % of scans were unreliable[12]. Patients were advised to be fasted for the examination[13]. Patients with a body mass index (BMI) of <35kg/m^2 underwent TE examination with the Fibroscan FS402 device (Echosens) M probe in the general practice setting. Due to a high risk of unreliable or failed liver stiffness acquisition with body mass index (BMI) measures above this threshold demonstrated in previous studies[14], patients with a

BMI>35kg/m^2, and those with an initial failed liver stiffness acquisition using the M probe, underwent transient elastography in the hospital using the Fibroscan FS502 device XL probe.

Liver stiffness acquisition failure was defined as inability to obtain 10 valid liver stiffness measurements. Participants with failure of liver stiffness acquisition were excluded from the analysis. A successful acquisition was deemed unreliable if liver stiffness was ≥7.1 kilopascals and the interquartile range/median ratio was greater than 0.3 as per manufacturer guidance[15]. A liver stiffness threshold of 8.0 kilopascals or greater was used to define elevated liver stiffness, and hence clinically significant liver disease, in keeping with a previous large general population study in France[16] in which this cut-off was shown to be an accurate predictor of liver fibrosis on biopsy. The same liver stiffness threshold was used for patients with both alcohol and non-alcohol related liver risk factor as although alcohol-related liver fibrosis potentially results in slightly higher liver stiffness results than NAFLD, a recent meta-analysis of previous hospital studies has shown good accuracy for predicting significant (F2) liver fibrosis in patients with alcoholic liver disease using very similar liver stiffness cutoffs[17].

Patients with elevated liver stiffness results, including high but unreliable acquisitions, were reviewed by a visiting consultant hepatologist in the community (one of authors SR, EW, MJ, GPA or ING). Alternative causes of chronic liver disease (e.g. viral and autoimmune liver disease) were tested for. In addition, at the clinical discretion of the reviewing hepatologist, further investigations including

ultrasonography, liver biopsy and endoscopy were arranged on a case-by-case basis.

Following the transient elastography appointment, patient's electronic primary care records were retrospectively examined to collect recent relevant clinical, anthropometric and laboratory test data (definitions of these risk factors are shown in Online Appendix 1). As waist circumference was not routinely measured, obesity was defined as the presence of body mass index≥30kg/m^2. Subsequently, metabolic syndrome was defined according to the International Diabetes Federation definition as presence of obesity with 2 or more metabolic risk factors (hypertension, impaired fasting glucose or type 2 diabetes, raised triglycerides or lowered high density lipoprotein cholesterol)[18].

Cirrhosis Detection and Associated Risk Factors

Cirrhosis was diagnosed clinically at the discretion of the visiting consultant hepatologist. To increase the positive predictive value of cirrhosis diagnoses, given the need for future cirrhosis surveillance investigations, cirrhosis diagnoses were not based upon an elevated liver stiffness measurement alone. Rather cirrhosis diagnoses were assigned using elevated liver stiffness measures in combination with either histological evidence of cirrhosis, endoscopic evidence of portal hypertension or ultrasound evidence of cirrhosis or portal hypertension (i.e. nodular liver surface, splenomegaly or reversal of portal vein flow). Cirrhosis diagnoses were classified as alcoholic liver disease if hazardous alcohol use was present in the absence of obesity or type 2 diabetes, as non-alcoholic fatty liver disease in the presence of type 2 diabetes or obesity, but without hazardous alcohol use, and as dual aetiology if a combination of hazardous alcohol use and type 2 diabetes or obesity was present.

The number and aetiology of cirrhosis diagnoses in the general practice population before study commencement were obtained by searching the electronic patient records.

To evaluate the impact of the defined clinical and metabolic risk factors on the presence of significant liver disease, we compared the percentage of elevated liver stiffness and cirrhosis cases for patients with and without these risk factors. Subgroup analyses examining patients with hazardous alcohol use, type 2 diabetes and both hazardous alcohol and type 2 diabetes were performed.

Statistics

Statistical analysis was performed using Stata version 13.1 (StataCorp LP). Categorical data are presented as number (percentage). Continuous data are presented as medians (range) (as all were non-normally distributed). Demographic, anthropometric and laboratory test data were compared between patients with and without cirrhosis using the Mann-Whitney test as appropriate. Categorical variables were compared using chi-squared test, or Fisher's exact test where appropriate.

In order to further evaluate the association of clinical and metabolic risk factors with clinically significant liver disease, for those risk factors which were associated with both presence of elevated liver stiffness and cirrhosis we report univariate odds ratios and 95% confidence intervals comparing patients with and without these clinical features in each of our studied groups.

Results

Study Population

The total adult population in the studied primary care centres at commencement of the study was 20,868 patients (see table 1). Hazardous alcohol use was detected in 1,438 patients (6.9%) and 1,007 patients (4.8%) had type 2 diabetes. There were 2,368 individual patients with hazardous alcohol use or type 2 diabetes identified from the electronic patient record search, of whom 346 were excluded (see Figure 1). Subsequently 919/2,022 patients (45.4%) attended the transient elastography appointment; 71.3% of eligible patients with type 2 diabetes attended whilst 30.7% of patients with hazardous alcohol use attended. Overall, 401 patients had hazardous alcohol use, 554 patients had type 2 diabetes (including 65 patients (7.1%) with both risk factors present), and 29 had raised ALT without either hazardous alcohol use or type 2 diabetes. Of note, of the hazardous alcohol use group, 17 (4.2% of the group) had subsequently become abstinent and a further 38 (9.5%) had moderated their alcohol intake to within recommended safe drinking limits prior to the time of TE.

Compared to non-attenders, transient elastography appointment attenders were significantly less likely to be hazardous alcohol users (43.6% vs. 83.0%; $p<0.001$), significantly less likely to be male (65.7% vs. 71.7%; $p=0.004$) and were significantly older (mean age 59.1 years vs. 47.8 years; $p<0.001$).

Elevated Liver Stiffness and Cirrhosis Diagnoses

Successful liver stiffness results were obtained in 899 patients (97.8% of those undergoing transient elastography). Of these, 819 (91.1%) liver stiffness acquisitions were obtained using the M probe in the primary care setting, whilst the remaining 80

patients required an XL probe examination in the hospital setting. Unreliable liver stiffness acquisitions occurred in 44 patients (4.9%).

Overall, elevated liver stiffness of ≥8 kilopascals was observed in 230 patients (25.6%). Elevated liver stiffness was present in 19.2% of patients with hazardous alcohol use, 31.5% of patients with type 2 diabetes, 37.5% of patients with both hazardous alcohol use and type 2 diabetes, and 45.3% of patients with raised ALT levels. On further testing a single case of primary biliary cholangitis in a patient with coexistent non-alcoholic steatohepatitis was identified. A large number of clinical and anthropometric risk factors were more prevalent in patients with elevated liver stiffness compared to normal liver stiffness values (see table 2). However, both hazardous alcohol use prevalence (47.3% vs. 32.6%; $p<0.001$) and median alcohol consumption (8 vs. 3 units of ethanol per week; $p<0.001$) were significantly lower in patients with elevated liver stiffness.

Prior to study commencement, there were 23 diagnosed cases of liver cirrhosis in the population of the studied general practices who were excluded from study. All cases had been diagnosed on the basis of histological evidence of liver cirrhosis, or presentation to hospital with decompensated liver cirrhosis. Their cirrhosis aetiologies were alcoholic liver disease (14 patients), Hepatitis B or C (5), NAFLD (1) and other (3).

During the study, 209 patients with elevated liver stiffness attended and were reviewed in hepatology clinics and 27 of these were newly diagnosed with liver cirrhosis during the study period (3% of valid liver stiffness results). This, therefore, more than doubled the number of cirrhosis diagnoses in the studied general practices. Cirrhosis was diagnosed in 2.8% of the overall study patients with

hazardous alcohol use, 3.7% of patients with type 2 diabetes, 7.7% of patients with both hazardous alcohol use and type 2 diabetes, and 5.6% of patients with raised ALT levels. Relevant clinical characteristics of these patients are displayed in Table 3. Cirrhosis aetiologies were NAFLD in 16 patients (59.3% of newly detected cirrhosis cases), alcoholic liver disease in 3 patients (11.1%) and risk factors for both ALD and NAFLD in the remaining 8 patients (29.6%). Definitive evidence of portal hypertension was found in 4 patients on further investigation (3 patients with small varices and 1 patient with ascites) and features suggestive of portal hypertension observed in 6 others (5 patients with splenomegaly and 1 patient with portal vein flow reversal on ultrasonography).

Compared to patients with normal liver stiffness, patients with cirrhosis had significantly greater prevalence of obesity (81.6% vs. 31.8%; p=<0.001), greater prevalence of metabolic syndrome (59.3% vs. 25.5%; p=0.002), and higher prevalence of raised ALT levels (33.3% vs 13.0%; p=0.006). Therefore, normal ALT values were seen in 66.7% of patients with cirrhosis.

The total number of patients with cirrhosis was 50 following the study, when considering known patients with cirrhosis pre-study (23 patients) and additional new diagnoses detected due to the study (27 patients). Overall 20 out of 1,007 known patients with type 2 diabetes in the studied general practices (2%), and 25 out of 1,438 known hazardous alcohol drinkers (1.7%) were known to have cirrhosis upon completion of the study.

Impact of Clinical Parameters on Elevated Liver Stiffness and Cirrhosis Diagnoses

A comparison of the clinical and anthropometric factors associated with elevated liver stiffness in the subgroups of patients with hazardous alcohol use, type 2 diabetes and both risk factors are displayed in Table 4. Variables associated with elevated liver stiffness in subgroups of patients with either hazardous alcohol use or type 2 diabetes were obesity ((44.0% vs. 20.3%; p<0.001) and (67.8% vs. 42.6%; p<0.001) respectively), body mass index measurement ((median BMI 28.7 vs. 25.7; p<0.001) and (median BMI 32.45 vs. 28.9; p<0.001) respectively), metabolic syndrome ((26.7% vs. 8.9%; p<0.001) and (63.7% vs. 42.9%; p<0.001) respectively) and raised ALT level ((33.3% vs. 13.3%; p<0.001) and (26.9% vs. 7.6%; p<0.001) respectively). In addition, BMI measurement was associated with elevated liver stiffness in patients with both hazardous alcohol use and type 2 diabetes (median BMI 32.75 vs. 28.05; p<0.001). Corresponding data for cirrhosis is not provided due to too small patient numbers with cirrhosis within the analysed subgroups.

Given their association with both elevated liver stiffness and cirrhosis diagnoses in the overall study population (tables 2 and 4), the impact of obesity, metabolic syndrome and raised ALT on the diagnosis of elevated liver stiffness and cirrhosis diagnoses were evaluated further for subgroups of 391 patients with hazardous alcohol use, 543 patients with type 2 diabetes and 64 patients with both of these risk factors.

Hazardous alcohol users with obesity were significantly more likely to have elevated liver stiffness than hazardous alcohol users without obesity (Odds Ratio 3.1; 95% CI 1.8-5.3), as were those with hazardous alcohol use and the metabolic syndrome (OR 3.7 (95% CI 2.0-7.1) or those with hazardous alcohol use and raised ALT levels (OR

3.3; 95% CI 1.8-5.8). Likewise patients with type 2 diabetes and obesity were significantly more likely to have elevated liver stiffness than non-obese patients with type 2 diabetes (OR 2.9; 95% CI 1.9-4.2), as were those with type 2 diabetes and the metabolic syndrome (OR 2.4; 95% CI 1.6-3.5) or those with type 2 diabetes and raised ALT levels (OR 4.5; 95% CI 2.7-7.5). No significant associations were seen in those patients with both hazardous alcohol use and type 2 diabetes for elevated liver stiffness (see Table 5a).

Hazardous alcohol users with obesity were significantly more likely to be diagnosed with cirrhosis than non–obese hazardous alcohol users (odds ratio 5.6; 95% CI 1.6-19.7; cirrhosis prevalence 7.3% vs. 1.4%), and similarly obese patients with type 2 diabetes were more likely to be so diagnosed than non-obese patients with type 2 diabetes (OR 9.4; 95% CI 2.2-40.9; 6.6% vs. 0.7%). Patients with hazardous alcohol use, type 2 diabetes and obesity had a cirrhosis prevalence of 13.3%, although this was not statistically significantly greater than patients with hazardous alcohol use and type 2 diabetes alone (OR 5.1; 95%CI 0.5-48.2). The associations with obesity are also displayed graphically in Figure 2. Patients with type 2 diabetes and the metabolic syndrome were significantly more likely to be diagnosed with cirrhosis than patients with type 2 diabetes without metabolic syndrome (OR 4.4; 95% CI 1.4-13.2; cirrhosis prevalence 6.0% vs. 1.4%). There were no significant associations between raised ALT levels and cirrhosis diagnoses in any of the studied groups (see table 5b).

Discussion

Key Findings

The current study investigates cirrhosis detection and risk factors for liver disease in primary care using transient elastography. Following screening of 919 patients with hazardous alcohol use, type 2 diabetes or raised ALT levels, using Transient Elastography and subsequent confirmative investigations, we identified 27 previously undiagnosed cases of cirrhosis, to supplement the 23 cases of cirrhosis that had been previously detected in this population. Hazardous alcohol users were less likely to attend and when they did, had a lower risk of cirrhosis than did diabetics. Grouping by risk factor we found that of those screened due to type 2 diabetes, a history of alcohol misuse or both 3.7%, 2.8% and 7.7% respectively were diagnosed with cirrhosis. When the risk factors were combined this resulted in a greater "yield" of detecting cirrhosis. For example, 6.6% of studied patients with both type 2 diabetes and obesity were diagnosed with cirrhosis, whilst 13.3% of patients with a combination of hazardous alcohol use, type 2 diabetes and obesity were cirrhotic.

Within each of these groups the risk of elevated liver stiffness was greater in patients with type 2 diabetes, metabolic syndrome or raised ALT. In those detected with cirrhosis, obesity was the critical factor, not ALT. For example, compared to non-obese patients, obese patients with hazardous alcohol use were 5.6 times more likely to be diagnosed with liver cirrhosis and obese patients with type 2 diabetes were 9.4 times more likely to be cirrhotic.

Strengths and Limitations

Hitherto, this is one of the largest studies to evaluate the performance of transient elastography in screening populations for liver disease in a community setting with

targeted risk factors. This allows us to study how simple risk factors can be combined to improve the detection of significant liver disease. We selected all available subjects with the relevant risk factors who were fit for screening and did not already have a liver disease diagnosis, in an attempt to limit selection bias. To maximise the generalisability of our results patients were recruited from both suburban and inner city primary care practices to provide a representative mixture. A further strength we believe is the clinical confirmation of cirrhosis diagnoses, for which we used additional supportive radiological, histological and endoscopic evidence. Although recent guidance has suggested that a liver stiffness reading of greater than 15 kilopascals is strongly suggestive of compensated cirrhosis[19], the positive predictive value of liver stiffness readings in the community may be lower than previous secondary care studies due to reduced disease prevalence. We therefore believe the cirrhosis diagnoses we have reported are robust.

One of the limitations however is that only 45% of the eligible population underwent the transient elastography examination, although this is a greater response rate than the other major UK primary care liver stratification study thus far reported, which enrolled only 35% of patients defined as at risk from their alcohol consumption[20]. There was however a response bias with screening attenders being older, more female and with a differing proportion of hazardous alcohol use and type 2 diabetes than non-attenders. It is therefore difficult to predict the incremental increase of cirrhosis which would be diagnosed if everyone invited had attended. A further limitation is that as we targeted only type 2 diabetes and alcohol misuse as risk factors, though we have been able to show that obesity is an important co-factor in each, we are unable to assess whether it is an important risk factor in its own right. Based upon this it is likely that we have screened the highest risk patients with

obesity within the population, but we will have not detected patients with clinically significant liver disease and obesity alone as a risk factor.

Comparison with other studies

Previous systematic reviews have highlighted the accuracy of transient elastography for stratifying fibrosis stage in secondary care populations with non-alcoholic fatty liver disease[21,22]. Our own group recently published a systematic review of 19 prior studies which stratified primary care populations for risk of liver disease with non-invasive biomarkers[23]. Variables reported to be independently associated with elevated liver stiffness or fibrosis included obesity and elevated body mass index measurements, both of which in the current study were associated with significantly higher risks of liver disease in each of our studied risk factor groups. Subsequent results published from the Rotterdam Study of 3,041 patients over 45 years of age screened for liver disease using transient elastography[24] showed that both BMI>30kg/m^2 and type 2 diabetes were significantly associated with liver stiffness ≥8kPa (risk factor prevalence compared to normal liver stiffness was 37.7% vs. 21.4% for obesity, and 33.7% vs 9.8% for type 2 diabetes, respectively). Two large epidemiological studies from the United Kingdom have previously demonstrated the important synergism between body mass index and alcohol in predicting cirrhosis development and liver-related mortality[7,8]. For example, one was a long term follow-up of 9,722 male workers from Scotland analysing the risk of liver-related mortality. Whilst mortality risk due to elevated body mass index (overweight or obese patients) was not significantly different from baseline (hazard ratio 1.29, 95% CI 0.60-2.80), and far less than risk attributable to alcohol (consumption ≥15 units per week) (hazard ratio 3.66, 95% CI 1.74-7.71), the interaction of both body mass index and

alcohol greatly exceeded the risk from either factor alone or the expected product of the two (hazard ratio 9.53, 95% CI 4.98-18.2)[8].

We found cirrhosis in 3.7% of the patients with type 2 diabetes we screened which is similar to previous studies which have used transient elastography in cohorts of type 2 diabetes[25-28]. In addition, two studies of patients with type 2 diabetes screened in a hospital setting have detected a far greater prevalence of cirrhosis than the current study. In a study of 392 patients with type 2 diabetes, Sporea et al[27] found that 13.8% of their clinic cohort had liver stiffness measures of 10.3 kilopascals or greater suggestive of cirrhosis. A large study of patients attending diabetes screening in hospital published by Kwok et al highlighted both the high liver disease prevalence and impact of obesity detected using transient elastography[29]. In this study; 8.1% of patients with type 2 diabetes and BMI<25kg/m^2 had elevated liver stiffness consistent with advanced fibrosis compared to 35.4% of patients with BMI>30kg/m^2. Also in this study 11.2% had liver stiffness >11.5 kilopascals (used as a cirrhosis cut-off). The high cirrhosis prevalence detected in these two studies is likely to be explained by a comparatively low liver stiffness threshold to define cirrhosis coupled with the lack of second line confirmatory investigations.

Recent studies have published results of patients with type 2 diabetes screened for liver disease in a primary care population[16,30,31]. Roulot et al[30] studied 705 patients with type 2 diabetes in France. Similar to our study, 2.1% of patients were diagnosed with cirrhosis, defined using a liver stiffness threshold of 13 kilopascals. Importantly, the 13 kilopascals threshold had a 100% sensitivity and negative predictive value for histological cirrhosis in 47 patients undergoing liver biopsy, albeit a lower positive predictive value of 55.6%. This indicates the importance of additional clinical

parameters (such as laboratory parameters, ultrasonography and liver biopsy) for such patients prior to enrolling them to cirrhosis surveillance regimes.

Implications

In real life clinical practice, patients will have multiple risk factors for chronic liver disease. For example, within this study 44% of our population undergoing TE had two or more of hazardous alcohol use, type 2 diabetes or obesity. Given this, and the synergism of these risk factors that the study highlights we feel that strictly dichotomising patients with alcoholic liver disease and NAFLD on the basis of a specific cut-off of alcohol consumption may serve to mislead. In our study patients with hazardous alcohol use, type 2 diabetes and obesity had a cirrhosis prevalence of 13.3%, and elevated liver stiffness was seen in 46.7%. However, when considering type 2 diabetes as the only selection criteria the equivalent figures were 3.7% and 31.5%. That the vast majority of significant liver disease detected was found in those with diabetes and/or obesity shows we think that alcohol alone is not likely to remain the cause of the majority of the emerging epidemic of liver disease in the United Kingdom in future.

Given the high prevalence of both elevated liver stiffness and cirrhosis detected in patients with type 2 diabetes, in addition to proof of concept of screening such patients using transient elastography in primary care, we believe that formal screening for liver disease in type 2 diabetes should now be considered. In addition to lifestyle alterations, early detection will allow optimal medication management of these individuals with antidiabetic medication which will also treat non-alcoholic steatohepatitis, such as pioglitazone[32] or liraglutide[33,34]. One option to increase the cost efficacy of this is for selective screening and surveillance based upon the type and number of risk factors, to ensure a high pre-test probability of identifying

clinically significant liver disease. In this study we have demonstrated that both hazardous alcohol use and obesity are potentially useful markers of higher risk groups for this purpose. Further optimisation of community-based liver disease detection strategy is required, both in terms of initial risk factor selection, and whether the addition of other simple liver fibrosis tests to primary care algorithms improves the classification of liver fibrosis[35]. Such work though we feel is now a priority to enable the eventual roll out of selective screening to detect liver disease at an earlier stage.

Summary

Using Transient Elastography to selectively screen for liver disease in primary care, and referring in high risk patients to a hepatology clinic resulted in a more than doubling of the number of cirrhosis cases diagnoses in the studied population. The majority of newly identified cirrhosis cases had type 2 diabetes and obesity as risk factors (and therefore, presumably had non-alcoholic fatty liver disease).The risk of cirrhosis was far higher in those with multiple risk factors (hazardous alcohol use, obesity and type 2 diabetes). Focussing upon the combination of liver disease risk factors is likely to be the most effective way of designing cost effective investigation algorithms, and relevant interventions, for patients in primary care.

References

1. Ratib S, West J, Crooks CJ, Fleming KM. Diagnosis of liver cirrhosis in England, a cohort study, 1998-2009: a comparison with cancer. *Am J Gastroenterol.* 2014;109(2):190-198.
2. Murray CJ, Richards MA, Newton JN, et al. UK health performance: findings of the Global Burden of Disease Study 2010. *Lancet.* 2013;381(9871):997-1020.
3. Rehm J, Samokhvalov AV, Shield KD. Global burden of alcoholic liver diseases. *J Hepatol.* 2013;59(1):160-168.
4. Wong RJ, Aguilar M, Cheung R, et al. Nonalcoholic steatohepatitis is the second leading etiology of liver disease among adults awaiting liver transplantation in the United States. *Gastroenterology.* 2015;148(3):547-555.
5. Ekstedt M, Franzen LE, Holmqvist M, et al. Alcohol consumption is associated with progression of hepatic fibrosis in non-alcoholic fatty liver disease. *Scand J Gastroenterol.* 2009;44(3):366-374.
6. Naveau S, Giraud V, Borotto E, Aubert A, Capron F, Chaput JC. Excess weight risk factor for alcoholic liver disease. *Hepatology.* 1997;25(1):108-111.
7. Liu B, Balkwill A, Reeves G, Beral V, Million Women Study C. Body mass index and risk of liver cirrhosis in middle aged UK women: prospective study. *BMJ.* 2010;340:c912.
8. Hart CL, Morrison DS, Batty GD, Mitchell RJ, Davey Smith G. Effect of body mass index and alcohol consumption on liver disease: analysis of data from two prospective cohort studies. *BMJ.* 2010;340:c1240.
9. Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of non-alcoholic fatty liver disease: practice Guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association. *Hepatology.* 2012;55(6):2005-2023.
10. Harman DJ, Ryder SD, James MW, et al. Direct targeting of risk factors significantly increases the detection of liver cirrhosis in primary care: a cross-sectional diagnostic study utilising transient elastography. *BMJ open.* 2015;5(4):e007516.
11. Saunders JB, Aasland OG, Babor TF, Delafuente JR, Grant M. Development of the Alcohol-Use Disorders Identification Test (Audit) - Who Collaborative Project on Early Detection of Persons with Harmful Alcohol-Consumption .2. *Addiction.* 1993;88(6):791-804.
12. McCorry RB, Palaniyappan N, Chivinge A, Kaye P, James MW, Aithal GP. Development and evaluation of a nurse-led transient elastography service for the staging of hepatic fibrosis in patients with suspected chronic liver disease. *QJM.* 2012;105(8):749-754.

13. Liver EAfSo, Higado ALpeEd. EASL-ALEH Clinical Practice Guidelines: Non-invasive tests for evaluation of liver disease severity and prognosis. *J Hepatol.* 2015;63(1):237-264.
14. Myers RP, Pomier-Layrargues G, Kirsch R, et al. Feasibility and diagnostic performance of the FibroScan XL probe for liver stiffness measurement in overweight and obese patients. *Hepatology.* 2012;55(1):199-208.
15. Echosens. Fibroscan Recommendations - Updated recommendations for a reliable Fibroscan liver stiffness measurement. 2013; http://asp-indus.secure-zone.net/v2/indexPop.jsp?id=955/1196/3761.
16. Roulot D, Costes JL, Buyck JF, et al. Transient elastography as a screening tool for liver fibrosis and cirrhosis in a community-based population aged over 45 years. *Gut.* 2011;60(7):977-984.
17. Pavlov CS, Casazza G, Nikolova D, et al. Transient elastography for diagnosis of stages of hepatic fibrosis and cirrhosis in people with alcoholic liver disease. *The Cochrane database of systematic reviews.* 2015;1:CD010542.
18. Zimmet P, KG MMA, Serrano Rios M. [A new international diabetes federation worldwide definition of the metabolic syndrome: the rationale and the results]. *Revista espanola de cardiologia.* 2005;58(12):1371-1376.
19. de Franchis R, Baveno VIF. Expanding consensus in portal hypertension: Report of the Baveno VI Consensus Workshop: Stratifying risk and individualizing care for portal hypertension. *J Hepatol.* 2015;63(3):743-752.
20. Sheron N, Moore M, Ansett S, Parsons C, Bateman A. Developing a 'traffic light' test with potential for rational early diagnosis of liver fibrosis and cirrhosis in the community. *Brit J Gen Pract.* 2012;62(602):470-471.
21. Festi D, Schiumerini R, Marzi L, et al. Review article: the diagnosis of non-alcoholic fatty liver disease -- availability and accuracy of non-invasive methods. *Aliment Pharmacol Ther.* 2013;37(4):392-400.
22. Kwok R, Tse YK, Wong GL, et al. Systematic review with meta-analysis: non-invasive assessment of non-alcoholic fatty liver disease--the role of transient elastography and plasma cytokeratin-18 fragments. *Aliment Pharmacol Ther.* 2014;39(3):254-269.
23. Harris R HD, Card TR, Aithal GP, Guha IN. Prevalence of clinically significant liver disease within the general population, as defined by non-invasive markers of liver fibrosis: a systematic review. *The Lancet Gastroenterology and Hepatology.* 2017;2(4):288-297.

24. Koehler EM, Plompen EP, Schouten JN, et al. Presence of diabetes mellitus and steatosis is associated with liver stiffness in a general population: The Rotterdam study. *Hepatology.* 2016;63(1):138-147.
25. Jacqueminet S, Lebray P, Morra R, et al. Screening for liver fibrosis by using a noninvasive biomarker in patients with diabetes. *Clin Gastroenterol Hepatol.* 2008;6(7):828-831.
26. Morling JR, Fallowfield JA, Guha IN, et al. Clinically significant chronic liver disease in people with Type 2 diabetes: the Edinburgh Type 2 Diabetes Study. *QJM.* 2016;109(4):249-256.
27. Sporea I, Mare R, Lupușoru R, et al. Liver Stiffness Evaluation by Transient Elastography in Type 2 Diabetes Mellitus Patients with Ultrasound-proven Steatosis. *J Gastrointestin Liver Dis.* 2016;25(2):167-174.
28. Kwok R, Choi KC, Wong GL, et al. Screening diabetic patients for non-alcoholic fatty liver disease with controlled attenuation parameter and liver stiffness measurements: a prospective cohort study. *Gut.* 2016;65(8):1359-1368.
29. Mortality GBD, Causes of Death C. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet.* 2016;388(10053):1459-1544.
30. Roulot D, Roudot-Thoraval F, NKontchou G, et al. Concomitant screening for liver fibrosis and steatosis in French type 2 diabetic patients using Fibroscan. *Liver Int.* 2017.
31. Doycheva I, Cui J, Nguyen P, et al. Non-invasive screening of diabetics in primary care for NAFLD and advanced fibrosis by MRI and MRE. *Aliment Pharmacol Ther.* 2016;43(1):83-95.
32. Aithal GP, Thomas JA, Kaye PV, et al. Randomized, placebo-controlled trial of pioglitazone in nondiabetic subjects with nonalcoholic steatohepatitis. *Gastroenterology.* 2008;135(4):1176-1184.
33. Armstrong MJ, Gaunt P, Aithal GP, et al. Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): a multicentre, double-blind, randomised, placebo-controlled phase 2 study. *Lancet.* 2015.
34. Noureddin M, Anstee QM, Loomba R. Review article: emerging anti-fibrotic therapies in the treatment of non-alcoholic steatohepatitis. *Aliment Pharmacol Ther.* 2016;43(11):1109-1123.
35. Petta S, Wong VW, Cammà C, et al. Serial combination of non-invasive tools improves the diagnostic accuracy of severe liver fibrosis in patients with NAFLD. *Aliment Pharmacol Ther.* 2017;46(6):617-627.

Conflicts of Interest:
All authors declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Funding Source/Sponsor:
Funding for study was provided by 2 sources i) the NIHR Nottingham Biomedical Research Centre, part of the University of Nottingham and Nottingham University Hospitals NHS Trust and ii) The East Midlands Academic Health Sciences Network (AHSN). The study sponsor is the University of Nottingham, who are data custodians but had no role in the design, analysis or interpretations of the data. All authors declare that they are free from other sources of external funding related to this study.

Authorship Statement:
DJ Harman, SD Ryder, MW James, EA Wilkes, TR Card, GP Aithal and IN Guha were involved in the study design and concept, implementation of the study in primary care, interpretation of results and editing of the manuscript. Additionally DJ Harman analysed the data set and wrote the initial manuscript draft. All authors, external and internal, had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis. All authors have approved the final version of the manuscript and authorship list. GP Aithal and IN Guha are guarantors.

ClinicalTrials.gov registration: NCT02037867

Tables

Table 1. Baseline characteristics of total adult patient population (n=20,868) at studied General Practice (GP) sites			
Variable	**Suburban GP Patients (n=10,479)**	**Inner City GP Patients (n=10,389)**	**P Value**
Age (n%)			
- 18-30 years	2100 (20.4%)	2640 (25.4%)	**<0.001**
- 31-40 years	2469 (23.6%)	2333 (22.5%)	0.06
- 41-50 years	1903 (18.2%)	1986 (19.1%)	0.08
- 51-60 years	1331 (12.7%)	1535 (14.8%)	**<0.001**
- 61-70 years	1287 (12.3%)	953 (9.2%)	**<0.001**
- 71-80 years	781 (7.5%)	606 (5.8%)	**<0.001**
->80 years	608 (5.8%)	346 (3.3%)	**<0.001**
Male Gender n(%)	5131 (49.0%)	5391 (51.2%)	**<0.001**
Body Mass Index n(%)			
- 25-29.9	2835 (27.1%)	4177 (40.2%)	**<0.001**
- ≥30	1320 (12.6%)	2527 (24.3%)	**<0.001**
- Missing values	1363 (13.0%)	995 (9.6%)	**<0.001**
Hazardous Alcohol Use n(%)	658 (6.3%)	780 (7.5%)	**<0.001**
Type 2 Diabetes n(%)	390 (3.7%)	617 (5.9%)	**<0.001**
Ischaemic Heart Disease n(%)	423 (4.0%)	406 (3.9%)	0.66
Hypertension n(%)	1521 (14.5%)	1356 (13.1%)	**0.002**
Hyperlipidaemia n(%)	2117 (20.2%)	1806 (17.4%)	**<0.001**

P value compares patients from Suburban primary care practices and Inner City practices; p values≤0.05 are statistically significant and are displayed in bold. GP = General Practice

Table 2. Clinical and laboratory test characteristics of 899 patients with successful liver stiffness measurement, comparing patients with normal liver stiffness (n=669) separately to patients with elevated liver stiffness (n=230) and patients with liver cirrhosis (n=27)					
Variable	**Normal Liver Stiffness (n=669)**	**Elevated Liver Stiffness (n=230)**	**P Value***	**Cirrhosis (n=27)**	**P Value$**
Age (years)	60.0 (48-69)	63.0 (52-70)	**0.02**	63.0 (55-67)	0.48
Male Gender n(%)	430 (74.4%)	161 (70.0%)	0.12	20 (74.1%)	0.36
Body Mass Index (kg/m^2)	27.4 (24.2-30.9)	31.6 (28.2-35.3)	**<0.001**	33.2 (30.4-36.3)	0.258
Hazardous Alcohol Use n(%)	316 (47.3%)	75 (32.6%)	**<0.001**	11 (40.7%)	0.77
Current alcohol (units/week)	8 (0-28)	3 (0-24)	**0.02**	2 (0-42)	0.90
Type 2 Diabetes n(%)	371 (55.5%)	171 (74.4%)	**<0.001**	20 (74.1%)	0.14
Raised ALT n(%)	87 (13.0%)	73 (31.7%)	**<0.001**	9 (33.3%)	**0.006**
Obesity n(%)	210 (31.8%)	140 (60.9%)	**<0.001**	22 (81.5%)	**<0.001**
Ischaemic Heart Disease n(%)	69 (10.3%)	38 (16.5%)	**0.01**	5 (18.2%)	0.291
Hypertension n(%)	269 (40.3%)	126 (54.8%)	**<0.001**	14 (51.9%)	0.41
Hyperlipidaemia n(%)	433 (64.8%)	176 (76.5%)	**<0.001**	16 (59.3%)	0.54
Metabolic Syndrome n(%)	170 (25.5%)	118 (51.3%)	**<0.001**	16 (59.3%)	**0.002**
Liver Stiffness Median (kPa)	5.1 (4.3-6.1)	11.2 (8.9-14.9)	**<0.001**	27.4 (21.3-48.8)$	**<0.001**

Normally distributed numerical variables are displayed as mean (standard deviation(SD)) and compared using the t test, non-normally distributed numerical variables are displayed as median(interquartile range) and compared using the Mann-Whitney test. Categorical variables are displayed as n(%) and compared using Fisher's Exact test. P values ≤0.05 are displayed in bold. *=p value comparing patients with elevated liver stiffness and normal liver stiffness, $=p value comparing patients with cirrhosis and normal liver stiffness. ALT = alanine aminotransferase, AST = aspartate aminotransferase, kPa = kilopascals.

Table 3. Laboratory test, imaging and histopathology results of 27 patients newly diagnosed with cirrhosis during study

Liver Disease Risk Factor*	Age	Liver Stiffness (kPa)	Platelet Count (10^9/L)	Clinical Features of CLD[¥]	Ultrasound Abnormality[$]	Histopathology	Endoscopy Abnormality
Obesity	64	11.7	323	H	No	Cirrhosis (NASH)	No
T2DM and Obesity[€]	67	14.7	214	H	No	Not Performed	No
T2DM and Obesity	49	15.8	211	H	No	Cirrhosis (NASH)	No
Alcohol, T2DM And Obesity	64	17.1	182	No	Splenomegaly (17cm)	Not Performed	Not Performed
Alcohol, T2DM and Obesity	67	18.2	309	No	No	Cirrhosis (NASH)	No
Alcohol, Obesity and T2DM	67	18.5	95	No	Cirrhosis (nodular liver), Splenomegaly (14cm)	Not Performed	No
T2DM and Obesity	63	21.3	169	H	Splenomegaly (16cm)	Cirrhosis (NASH)	No
T2DM and Obesity	55	21.3	260	S	No	Cirrhosis (NASH)	No
T2DM and Obesity	68	24.0	143	No	No	Cirrhosis (NASH)	No
T2DM and Obesity	72	26.4	274	H	Cirrhosis (Coarse echotexture of the liver)	Not Performed	Not Performed
Alcohol And Obesity	58	27.0	123	H	Cirrhosis (Nodular liver)	Not Performed	No
T2DM And Obesity	67	27.0	131	S	No	Cirrhosis (NASH)	No
Alcohol and T2DM	48	27.0	339	No	No	Cirrhosis (ASH/NASH)	Grade 1 Varices
T2DM	65	27.4	235	No	No	Cirrhosis (NASH)	No

T2DM and Obesity	57	35.3	136	No	Cirrhosis (Nodular liver)	Cirrhosis (NASH)	Not Performed
T2DM and Obesity	52	36.3	147	H,S	Splenomegaly (17cm)	Not Performed	No
Alcohol	38	42.9	169	S	Cirrhosis (Nodular liver)	Not Performed	Not Performed
T2DM and Obese	58	44.3	116	H	Cirrhosis (Coarse echotexture of the liver), splenomegaly (14cm)	Cirrhosis (NASH)	Grade 1 Varices
Alcohol and Obesity	54	46.4	103	H,S	Cirrhosis (Nodular liver)	Not Performed	No
Alcohol, T2DM and Obesity	63	46.4	151	H	No	Not Performed	Not Performed
T2DM And Obesity	68	48.8	144	No	Splenomegaly (13cm)	Not Performed	Not Performed
T2DM And Obesity	65	49.6	356	H	No	Not Performed	PHG
T2DM And Obesity	75	50.5	109	No	Cirrhosis (Coarse echotexture of the liver), Splenomegaly (14cm)	Not Performed	Not Performed
Alcohol	55	52.3	81	H,S	Cirrhosis (Nodular liver), Reversal of portal vein flow	Not Performed	Not Performed
Alcohol	56	60.8	177	S	Cirrhosis (Nodular liver)	Not Performed	No
T2DM and Obesity	73	72	260	No	Cirrhosis (Nodular liver)	Not Performed	No
Alcohol and Obesity	49	75	139	S	Cirrhosis (Nodular liver), Trace of ascites	Not Performed	Grade 1 Varices

*Patients with alcohol excess as risk factor without obesity or type 2 diabetes were assigned diagnosis of cirrhosis due to alcoholic liver disease. Patients with type 2 diabetes or obesity without alcohol excess were assigned diagnosis of cirrhosis due to NASH. ¥Clinical features of chronic liver disease (CLD) – H = hepatomegaly, S = spider naevi. $Ultrasound abnormality refers to features suggestive of liver cirrhosis, rather than non-specific findings e.g. echotexture consistent with fatty liver infiltration/steatosis. €Due to patient body mass index of 54 and difficulty with subsequent investigations, Enhanced liver fibrosis (ELF) score of 12.392 was used as confirmation of cirrhosis. kPa = kilopascals, NASH = non-alcoholic steatohepatitis, PHG = portal hypertensive gastropathy, T2DM = type 2 diabetes.

Table 4. Clinical and laboratory test characteristics of 899 patients with successful liver stiffness measurement (LSM), comparing clinical features of patients with normal and elevated liver stiffness in risk factor groups of hazardous alcohol use (n=391), type 2 diabetes (n=542) and those with both hazardous alcohol use and type 2 diabetes (n=64)						
Variable	**Alcohol and Normal LSM (n=316)**	**Alcohol and Elevated LSM (n=75)**	**T2DM and Normal LSM (n=371)**	**T2DM and Elevated LSM (n=171)**	**Both risks and Normal LSM (n=40)**	**Both risks and Elevated LSM (n=24)**
Age (years)	55 (43-64)	61 (52-66)*	64 (56-74)	65 (54-71)	64.5 (57.5-72.5)	63 (56-67)
Male Gender n(%)	238 (75.3%)	65 (86.7%)	221 (59.6%)	115 (67.3%)	35 (87.5%)	22 (91.7%)
Body Mass Index (kg/m^2)	25.7 (22.8-28.7)	28.7 (26.5-33.3)*	28.9 (25.9-32.0)	32.45 (29.0-36.3)¥	28.05 (26.0-31.7)	32.75 (27.85-35.9)β
Hazardous Alcohol Use n(%)	-----	-----	40 (10.8%)	24 (14.0%)	-----	-----
Current alcohol (units/week)	28 (21-42)	30 (23-60)	0.5 (0-6)	1 (0-7)	25 (20-30)	29 (20.5-46)
Type 2 Diabetes n(%)	40 (12.7%)	24 (32.0%)*	-----	-----	-----	-----
Raised ALT level n(%)	42 (13.3%)	25 (33.3%)*	28 (7.6%)	46 (26.9%)¥	4 (10.0%)	6 (25.0%)
Obesity n(%)	63 (20.3%)	33 (44.0%)*	157 (42.6%)	116 (67.8%)¥	16 (40.0%)	14 (58.3%)
Ischaemic Heart Disease n(%)	18 (5.7%)	10 (13.3%)*	55 (14.8%)	31 (18.1%)	5 (12.5%)	3 (12.5%)
Hypertension n(%)	78 (24.8%)	38 (50.7%)*	209 (56.3%)	101 (59.1%)	22 (55.0%)	16 (66.7%)
Hyperlipidaemia n(%)	143 (45.3%)	40 (53.3%)	318 (85.7%)	149 (87.1%)	34 (85.0%)	17 (70.8%)
Metabolic Syndrome n(%)	28 (8.9%)	20 (26.7%)*	157 (42.3%)	109 (63.7%)¥	15 (37.5)	12 (50.0%)
Liver Stiffness Median (kPa)	4.8 (4.1-5.75)	10.9 (9.0-15.7)*	5.3 (4.4-6.4)	11.3 (9.0-15.8) ¥	5.1 (4.4-6.4)	12.85 (9.1-17.65) β

Normally distributed numerical variables are displayed as mean (standard deviation(SD)) and compared using the t test, non-normally distributed numerical variables are displayed as median(interquartile range) and compared using the Mann-Whitney test. Categorical variables are displayed as n(%) and compared using Fisher's Exact test. P values ≤0.05 are displayed in bold. *= p value comparing normal and elevated liver stiffness in patients with hazardous alcohol use; ¥ = p value comparing normal and elevated liver stiffness in patients with type 2 diabetes; β= p value comparing normal and elevated liver stiffness in patients with both of these risk factors. ALT = alanine aminotransferase, kPa = kilopascals, LSM = liver stiffness measurement.

Table 5a. Odds ratios for presence of elevated liver stiffness comparing presence and absence of obesity, metabolic syndrome and raised ALT level in patients with hazardous alcohol use (n=391), type 2 diabetes (n=543) or both hazardous alcohol and type 2 diabetes (n=64)

Variable	Hazardous Alcohol Use (n=391)			Type 2 Diabetes (n=543)			Hazardous Alcohol and Type 2 Diabetes (n=64)		
	Exposed	**Non-exposed**	**OR (95%CI)**	**Exposed**	**Non-exposed**	**OR (95%CI)**	**Exposed**	**Non-exposed**	**OR (95%CI)**
Obesity	33/96	42/290	**3.1 (1.8-5.3)**	116/273	55/267	**2.9 (1.9-4.2)**	14/30	10/34	2.1 (0.8-5.9)
Metabolic Syndrome	20/48	55/343	**3.7 (2.0-7.1)**	109/266	62/276	**2.4 (1.6-3.5)**	12/27	12/37	1.7 (0.6-4.6)
Raised ALT level	25/67	50/324	**3.3 (1.8-5.8)**	46/74	125/469	**4.5 (2.7-7.5)**	6/10	18/54	3.0 (0.8-12.0)

Table 5b. Odds ratios for presence of cirrhosis comparing presence and absence of obesity, metabolic syndrome and raised ALT level in patients with hazardous alcohol use (n=391), type 2 diabetes (n=543) or both hazardous alcohol and type 2 diabetes (n=64)

Variable	Hazardous Alcohol Use (n=391)			Type 2 Diabetes (n=543)			Hazardous Alcohol and Type 2 Diabetes (n=64)		
	Exposed	**Non-exposed**	**OR (95%CI)**	**Exposed**	**Non-exposed**	**OR (95%CI)**	**Exposed**	**Non-exposed**	**OR (95%CI)**
Obesity	7/96	4/290	**5.6 (1.6-19.7)**	18/273	2/268	**9.4 (2.2-40.9)**	4/30	1/34	5.1 (0.5-48.2)
Metabolic Syndrome	3/48	8/343	2.8 (0.7-10.9)	16/266	4/277	**4.4 (1.4-13.2)**	3/27	2/27	2.2 (0.3-14.1)
Raised ALT level	4/67	7/324	2.9 (0.8-10.1)	5/74	15/469	2.2 (0.8-6.2)	1/10	4/54	1.4 (0.1-13.9)

ALT = alanine aminotransferase; CI = confidence interval, OR = odds ratio; odds ratios reaching statistical significance are displayed in bold

Figure Legends

Figure 1 – Flowchart of 2,368 patients identified with risk factor for chronic liver disease through the transient elastography screening pathway

Figure 2 – Comparison of cirrhosis prevalence between obese and non-obese patients in risk factor groups of hazardous alcohol use (n=386), type 2 diabetes (n=541) and patients with both hazardous alcohol use and type 2 diabetes (n=64).