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

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Summary

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 kPa. Cirrhosis was confirmed by established histological, radiological and biochemical methods.

Results: Two thousand three hundred and sixty eight 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 eight (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.

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1 | 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 US 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 diagnoses6 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 men 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 this 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.

2 | MATERIALS AND METHODS

2.1 | Study setting

This was a cross-sectional study with recruitment from four general medical practices in Nottingham, United Kingdom. Of these, two primary care medical practices were located in an affluent suburban borough, whilst the remaining two 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 are 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 are 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.

2.2 | Patient selection

Patient selection for this 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:

1. Hazardous alcohol use—this was defined as presence of any of (1) >14 units per week ethanol consumption for women or >21 units per week ethanol consumption for men, (2) alcohol AUDIT questionnaire score ≥811 or (3) 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.

2. 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 (>35 IU/L for women, >45 IU/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 (1) there was definitive evidence of hepatic fibrosis or cirrhosis already identified from previous investigations, (2) there was a contraindication to transient elastography (pregnancy, indwelling cardiac device), (3) they had metastatic malignancy, (4) they were unable to consent to investigation due to significant cognitive impairment or (5) they were house-bound and could not attend the community practice. In addition, patients who presented with symptoms of decompensated liver cirrhosis (eg, 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.

2.3 | 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. 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. Patients were advised to be fasted for the examination. Patients with a body mass index (BMI) of <35 kg/m² 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, patients with a BMI>35 kg/m², 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 kPa and the interquartile range/median ratio was greater than 0.3 as per manufacturer guidance. A liver stiffness threshold of 8.0 kPa 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 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.

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 (eg, viral and autoimmune liver disease) were tested for. In addition, at the clinical discretion of the reviewing hepatologist, further investigations including ultrasound, 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 S1). As waist circumference was not routinely measured, obesity was defined as the presence of body mass index ≥30 kg/m². 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).

2.4 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 (ie, 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.

2.5 Statistics
Statistical analysis was performed using STATA version 13.1 (STATA Corp LP, USA). 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.

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.

3 RESULTS
3.1 Study population
The total adult population in the studied primary care centres at commencement of the study was 20868 patients (Table 1). Hazardous alcohol use was detected in 1438 patients (6.9%) and 1,007 patients (4.8%) had Type 2 diabetes. There were 2368 individual patients with hazardous alcohol use or Type 2 diabetes identified from the electronic patient record search, of whom 346 were
excluded (Figure 1). Subsequently 919/2022 patients (45.4%) attended the transient elastography appointment; 71.3% of eligible patients with Type 2 diabetes attended while 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 < .001), significantly less likely to be male (65.7% vs 71.7%; P = .004) and were significantly older (mean age 59.1 years vs 47.8 years; P < .001).

### 3.2 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 kPa 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 (Table 2). However, both hazardous alcohol use prevalence (47.3% vs 32.6%; P < .001) and median alcohol consumption (8 vs 3 units of ethanol per week; P < .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

### 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 %) (y)                   |                                   |                                     |         |
| 18-30                           | 2100 (20.4%)                      | 2640 (25.4%)                        | <.001   |
| 31-40                           | 2469 (23.6%)                      | 2333 (22.5%)                        | .06     |
| 41-50                           | 1903 (18.2%)                      | 1986 (19.1%)                        | .08     |
| 51-60                           | 1331 (12.7%)                      | 1535 (14.8%)                        | <.001   |
| 61-70                           | 1287 (12.3%)                      | 953 (9.2%)                          | <.001   |
| 71-80                           | 781 (7.5%)                        | 606 (5.8%)                          | <.001   |
| ≥80                             | 608 (5.8%)                        | 346 (3.3%)                          | <.001   |
| Male Gender n (%)               | 5131 (49.0%)                      | 5391 (51.2%)                        | <.001   |
| Body mass index n (%)           |                                   |                                     |         |
| 25-29.9                         | 2835 (27.1%)                      | 4177 (40.2%)                        | <.001   |
| ≥30                             | 1320 (12.6%)                      | 2527 (24.3%)                        | <.001   |
| Hazardous alcohol use n (%)     | 658 (6.3%)                        | 780 (7.5%)                          | <.001   |
| Type 2 diabetes n (%)           | 390 (3.7%)                        | 617 (5.9%)                          | <.001   |
| Ischaemic heart disease n (%)   | 423 (4.0%)                        | 406 (3.9%)                          | .66     |
| Hypertension n (%)              | 1521 (14.5%)                      | 1356 (13.1%)                        | .002    |
| Hyperlipidaemia n (%)           | 2177 (20.2%)                      | 1806 (17.4%)                        | <.001   |

P value compares patients from Suburban primary care practices and Inner City practices; P ≤ .05 are statistically significant and are displayed in bold.

GP, General Practice.
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 (three patients with small varices and one patient with ascites) and features suggestive of portal hypertension observed in six others (five 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%; \( P \leq .001 \)), greater prevalence of metabolic syndrome (59.3% vs 25.5%; \( P = .002 \)), and higher prevalence of raised ALT levels (33.3% vs 13.0%; \( P = .006 \)). 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 prestudy (23 patients) and additional new diagnoses detected due to the study (27 patients). Overall 20 of 1007 known patients with Type 2 diabetes in the studied general practices (2%), and 25 of 1,438 known hazardous alcohol drinkers (1.7%) were known to have cirrhosis upon completion of the study.

### 3.3 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%; \( P < .001 \)) and (67.8% vs 42.6%; \( P < .001 \)) respectively, body mass index measurement (median BMI 28.7 vs 25.7; \( P < .001 \)) and (median BMI 32.45 vs 28.9;...
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 (Table 5b).

### Discussion

#### Key findings

This 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

### 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 valueb |
|---------------------------|----------------------------------|-----------------------------------|----------|--------------------|----------|
| Age (y)                   | 60.0 (48-69)                     | 63.0 (52-70)                      | .02      | 63.0 (55-67)       | .48      |
| Male Gender n (%)         | 430 (74.4%)                      | 161 (70.0%)                       | .12      | 20 (74.1%)         | .36      |
| Body mass index (kg/m²)   | 27.4 (24.2-30.9)                 | 31.6 (28.2-35.3)                  | <.001    | 33.2 (30.4-36.3)   | .258     |
| Hazardous alcohol use n (%) | 316 (47.3%)                     | 75 (32.6%)                       | <.001    | 11 (40.7%)         | .77      |
| Current alcohol (units/week) | 8 (0-28)                         | 3 (0-24)                          | .02      | 2 (0-42)           | .90      |
| Type 2 diabetes n (%)     | 371 (55.5%)                      | 171 (74.4%)                      | <.001    | 20 (74.1%)         | .14      |
| Raised ALT n (%)          | 87 (13.0%)                       | 73 (31.7%)                       | <.001    | 9 (33.3%)          | .006     |
| Obesity n (%)             | 210 (31.8%)                      | 140 (60.9%)                      | <.001    | 22 (81.5%)         | <.001    |
| Ischaemic heart disease n (%) | 69 (10.3%)                      | 38 (16.5%)                       | .01      | 5 (18.2%)          | .291     |
| Hypertension n (%)        | 269 (40.3%)                      | 126 (54.8%)                      | <.001    | 14 (51.9%)         | .41      |
| Hyperlipidaemia n (%)     | 433 (64.8%)                      | 176 (76.5%)                      | <.001    | 16 (59.3%)         | .54      |
| Metabolic syndrome n (%)  | 170 (25.5%)                      | 118 (51.3%)                      | <.001    | 16 (59.3%)         | .002     |
| Liver stiffness median (kPa) | 5.1 (4.3-6.1)                  | 11.2 (8.9-14.9)                  | <.001    | 27.4 (21.3-48.8)b  | <.001    |

*P value comparing patients with elevated liver stiffness and normal liver stiffness. 

bP value comparing patients with cirrhosis and normal liver stiffness. ALT, alanine aminotransferase, AST, aspartate aminotransferase, kPa, kilopascals.

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 (inter quartile 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.
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,
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 (y)                           | 55 (43-64)                       | 61 (52-66)a                      | 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/m²)           | 25.7 (22.8-28.7)                 | 28.7 (26.5-33.3)a                | 28.9 (25.9-32.0)           | 32.45 (29.0-36.3)b              | 28.05 (26.0-31.7)                | 32.75 (27.85-35.9)c              |
| 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)a                 | 5.3 (4.4-6.4)               | 11.3 (9.0-15.8)b                | 5.1 (4.4-6.4)                    | 12.85 (9.1-17.65)c               |

Normally distributed numerical variables are displayed as mean (standard deviation [SD]) and compared using the t test; non-normally distributed 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.

ALT, alanine aminotransferase, kPa, kilopascals, LSM, liver stiffness measurement.

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.

P value comparing normal and elevated liver stiffness in patients with both of these risk factors.

TABLE 5 Odds ratios for presence of (a) elevated liver stiffness and (b) 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)

| (a) 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) |

| (b) 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.

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.

4.2 | 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 kPa is strongly suggestive of compensated cirrhosis, 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. 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 in 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.

4.3 | 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. 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. Variables reported to be independently associated with elevated liver stiffness or fibrosis included obesity and elevated body mass index measurements, both of which in this 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 3041 patients over 45 years of age screened for liver disease using transient elastography showed that both BMI > 30 kg/m² and Type 2 diabetes were significantly associated with liver stiffness ≥ 8 kPa (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. For example, one was a long-term follow-up of 9722 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

| Odds Ratio (95% Confidence Interval) |
|--------------------------------------|
| Alcohol (not obese) (n = 290)        |
| Alcohol (obese) (n = 96)             |
| Type 2 Diabetes (not obese) (n = 268) |
| Type 2 Diabetes (obese) (n = 273)    |
| Alcohol and Diabetes (not obese) (n = 34) |
| Alcohol and Diabetes (obese) (n = 30) |

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)
Sporea et al. found that 13.8% of their clinic cohort had liver stiffness greater than this study. In a study of 392 patients with Type 2 diabetes, 11.2% had liver stiffness. Two studies of patients with Type 2 diabetes screened in a primary care population have detected a far greater prevalence of cirrhosis than this study. In a study of 392 patients with Type 2 diabetes, Sporea et al. found that 13.8% of their clinic cohort had liver stiffness measures of 10.3 kPa 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. In this study, 8.1% of patients with Type 2 diabetes and BMI > 25 kg/m² had elevated liver stiffness consistent with advanced fibrosis compared to 35.4% of patients with BMI > 30 kg/m². Also in this study, 11.2% had liver stiffness > 11.5 kPa (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. Roulot et al. 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 kPa. Importantly, the 13 kPa 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.

4.4 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 or liraglutide. 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. 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.

5 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.

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SUPPORTING INFORMATION

Additional Supporting Information will be found online in the supporting information tab for this article.

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