

The identification of chronic liver disease in primary care using non-invasive diagnostics within a novel pathway

Dr David Harman
Student ID: 4178136

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PhD Supervisors: Dr Neil Guha, Professor Guruprasad Aithal, Dr Tim Card, Dr Manpreet Bains

Abstract

Introduction: Deaths due to chronic liver disease have increased significantly in recent decades. This is due to increases in alcohol consumption and obesity during this time period, and insensitive screening tests (liver function blood tests) utilised in primary care. This thesis describes a new liver disease community diagnostic pathway which focussed upon defined risk factors for chronic liver disease and uses Transient Elastography (TE) as the primary investigation modality. The aims of the thesis are to assess the feasibility of this pathway for detecting liver disease due to alcohol or non-alcoholic fatty liver disease within the United Kingdom healthcare system, to quantify the number of new cases detected with this approach and to evaluate patient experience of these investigations.

Methods: Following a systematic review of the literature, an investigation pathway was derived and piloted in 4 general practice sites in Nottinghamshire in two phases between February 2012 and September 2014. Patients with hazardous alcohol use, type 2 diabetes or persistently raised alanine aminotransferase (ALT) level and negative liver serology were eligible for study. TE was performed in the community; a liver stiffness reading of ≥8 kilopascals defined clinically significant liver disease and subsequent review in a consultant led community clinic. Risk factors for new diagnoses of liver disease and cirrhosis were identified and the association with obesity investigated. A qualitative interview substudy was conducted to explore the experiences of 20 patients undergoing investigation.

Results: In a total adult population of 20,868 patients, 2,022 patients were eligible for study of whom 909 (45%) underwent TE. Valid liver stiffness measurements were possible in 98% of patients. Overall, 230 cases of elevated liver stiffness and 27 new cases of cirrhosis were identified. Minimum cirrhosis prevalence in patients with type 2 diabetes was 2%. Obesity was significantly associated with diagnosis of cirrhosis in type 2 diabetics (odds ratio 9.4 (95% CI 2.2-40.9)) and hazardous alcohol users (OR 5.6 (95% CI 1.6-19.7)). The majority of new cases of liver disease had normal ALT levels. From the initial pilot phase in two general practices in Rushcliffe (Nottingham), in which liver function test data from 378 patients undergoing TE was analysed, 72.4% with elevated liver stiffness measurement, 60% with biopsy proven cirrhosis and 90% with cirrhosis diagnosis had normal ALT. Patients felt that TE was a useful adjunct to lifestyle change and described a positive experience of liver disease investigation.

Conclusion: A new non-invasive diagnostic pathway for liver disease was feasible to implement in Nottinghamshire primary care and resulted in

significantly increased diagnosis of chronic liver disease and cirrhosis. These findings warrant exploration of the pathway in a larger primary care population.

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Chapter 1: Introduction

The introductory chapter of this thesis describes the epidemiology and natural history of liver cirrhosis, including further explanation of the two commonest cirrhosis aetiologies in the United Kingdom (alcoholic liver disease (ALD) and non-alcoholic fatty liver disease (NAFLD), the common investigations utilised to investigate suspected liver disease in primary and secondary care, and the rationale for why early identification of liver disease in primary care would improve current investigation algorithms.

Epidemiology of Chronic Liver Disease

Cirrhosis and Portal Hypertension

Any chronic insult to the liver may result in a cycle of inflammation, cell death and scarring (liver fibrosis). Over at least several years, ongoing insult may lead to progression of liver scarring with bridges of scar tissue forming between previously separate areas of liver fibrosis; this is a pathological stage of improved structural integrity of fibrosis at which reversibility following removal of the underlying insult is more difficult. Cirrhosis is the histological endpoint of all chronic liver diseases, defined by islands of regenerating liver cells separated by dense fibrous bands(1). As outlined below in clinical practice cirrhosis has a variable natural history depending on the presence of symptoms of liver failure or portal hypertension. Compensated cirrhosis can be defined as histological, radiological or biochemical evidence of nodular hepatic parenchyma secondary to accumulated liver fibrosis, whilst retaining enough functional liver reserve to perform expected metabolic functions. Importantly,

compensated cirrhosis is an asymptomatic phase and therefore not straightforward to detect.

Portal hypertension (development of portal venous pressure ≥6mmHg) is the watershed moment in the natural history of cirrhosis. Development of portal hypertension is a multifactorial process. Firstly, intrahepatic vascular resistance results from both structural obstruction to flow from nodular liver transformation (70%) and functional obstruction to flow resulting from a reduction of intrahepatic vasodilators, which is a reversible phenomenon(2). Secondly, total portal venous inflow rises due to an increase in vasodilator function in the splanchnic circulation, and subsequent increased splanchnic blood flow(2). Thirdly, angiogenesis (the development of new blood vessels) in response to both hepatic fibrogenesis and increased hepatic intravascular resistance plays an important role, albeit one which to date has not been fully quantified(3). The severity of portal hypertension, which can be quantified indirectly via measurement of the Hepatic Venous Pressure Gradient (HVPG), is an important predictor of future cirrhosis complications(4, 5). The development of any such complications of cirrhosis (most commonly ascites, encephalopathy, variceal bleeding or jaundice), subsequently marks the transition from compensated to decompensated cirrhosis(6, 7). The prognosis of patients with compensated and decompensated cirrhosis is markedly different.

The BAVENO classification is a prognostic tool defined by data from 2 large natural history studies of 1,649 cirrhotic patients from Italy(1), and distinguishes 4 stages of cirrhosis based upon features of portal

hypertension. Compensated cirrhosis corresponds to stages 1 and 2, which represent absence of portal hypertension sequelae, and presence of varices which haven't bled respectively. Recent publication of data concerning nearly 5,000 UK cirrhosis patients identified from the Clinical Practice Research Database (CPRD) has revealed that in the UK compensated cirrhosis patients have a significantly increased risk of mortality compared to the general population (Hazard Ratio (HR) 4.7, 95% CI 4.4-5.0)(8), and absolute risk of death one year from diagnosis was 7.2% (stage 1) and 6.6% (stage 2)(9).

Decompensated cirrhosis corresponds to stages 3 and 4 of the BAVENO classification; stage 3 is the development of ascites (fluid accumulation within the peritoneal cavity) and stage 4 refers to the onset of variceal bleeding. Decompensated cirrhosis heralds a marked increased risk of mortality. In the Italian BAVENO derivation studies, decompensated cirrhosis patients had rather bleak one year mortality rates of 20% for stage 3 and 57% for stage 4 respectively(1). It is important to note that these aforementioned studies used patients originally diagnosed in Sicily in the 1970s; variceal bleeding management in particular has improved significantly in this time with utilisation of variceal banding ligation, vasoactive drugs, antibiotic therapy and non-selective beta blockers(10). Nonetheless, UK CPRD data confirm the importance of hepatic decompensation as defined by BAVENO(9); mortality in the first year following diagnosis was 20.1% and 18.2% for BAVENO stages 3 and 4 respectively. However, subsequent CPRD analysis revealed that 47% of patients are diagnosed with cirrhosis

upon presenting to hospital with their first decompensation episode(11) and mortality of patients hospitalised with cirrhosis is significantly increased compared to those who remain ambulatory (adjusted HR 2.78, 95%CI 2.53-3.06) even when adjusted for BAVENO stages. Therefore, it is plausible that strategies focussing upon earlier identification of compensated cirrhosis may allow early interventions that slow down the transition to decompensated cirrhosis, potentially improving the survival. These interventions include varices surveillance via oesophagogastroduodenoscopy, and subsequent variceal ligation or institution of non-selective beta blocker therapy upon discovery of clinically significant varices(12), and hepatocellular carcinoma surveillance with abdominal ultrasound(13).

Cirrhosis Incidence, Prevalence and Mortality

Chronic liver disease continues to be a significant health problem worldwide. In 2010, alcohol-related cirrhosis alone was responsible for 493,300 deaths, or 0.9% of all-cause worldwide mortality(14). Using 2010 data collected by the World Health Organisation, Blachier et al found that 1.8% of deaths in Western Europe were due to cirrhosis of any aetiology(15). Liver disease mortality trends are particularly concerning in the United Kingdom. In contrast to many European countries (particularly the Mediterranean) liver disease mortality is rising in the UK, a trend which is considered partly driven by population alcohol consumption patterns(16). When considering cancer deaths as a single group, liver disease is presently the fifth most common cause of mortality in the United Kingdom, and unlike the other top ten causes the mortality is rising(17, 18). Worryingly, liver

disease causes excess mortality in the young and is the 3rd leading cause of premature mortality (in people aged 20-54 years) after cardiovascular disease and accidents(19). Furthermore deaths due to cirrhosis in the UK have increased by approximately 20% in the under 65s(17). Unsurprisingly, between the most recent two decades UK liver disease mortality has become rather geographically distinct, with an excess of mortality in the North of the country compared to the South(17). This mirrors the distribution of both alcohol consumption and obesity in the UK, and these co-factors are likely the explanation for this phenomenon.

The most common aetiologies of chronic liver disease in the United Kingdom are alcohol-related liver disease, non-alcoholic fatty liver disease (NAFLD; closely linked to metabolic syndrome risk factors) and chronic viral hepatitis(15, 17). All of these aetiologies predominantly result from lifestyle-related risk factors, and are therefore potentially preventable causes of disease. Unfortunately, alcohol consumption and obesity, as discussed in subsequent sections, are growing population epidemics which are strongly contributing to rising cirrhosis incidence and mortality. Fleming et al compared cirrhosis incidence and prevalence in the UK between 1992 and 2001 using data from the CPRD(20). They identified 3,360 patients with incident cirrhosis during this time period, with alcohol the most common causative agent and attributable to at least 35.9% of cirrhosis cases. During the follow-up period, cirrhosis incidence increased by 45% and cirrhosis prevalence increased by 68%. This study also provides the most recent estimate of cirrhosis prevalence in the UK of 76.3 cases per 100,000

populations, or 0.076%. Cirrhosis incidence estimates were recently updated by the same researchers, by combining data from the CPRD and Hospital Episode Statistics (HES) and comparing cirrhosis incidence between 1998 and 2009(21). UK cirrhosis incidence increased further during this time period (50.6%). Interestingly, percentage increase in alcohol-related cirrhosis was lower than non-alcoholic cirrhosis in men (40% vs. 79%) but higher in women (53% vs. 48%). Nonetheless, alcohol still accounted for a greater proportion of cirrhosis cases in men than women (61.9% vs. 42.8%, $p<0.001$). Highlighting the continued significance of the cirrhosis burden, in 2009 cirrhosis incidence was greater than the 5th leading cancer (Non-Hodgkin's Lymphoma) and only melanoma and thyroid cancers had a greater increase in incidence over the entire study period.

Alcohol-related Liver Disease

The total recorded alcohol consumption in the United Kingdom doubled between 1950 and 2002(16), which was closely mirrored by a more than 400% increase in standardised mortality ratio for cirrhosis during the same time period(16, 22). Between 1991 and 2005, deaths directly attributed to alcohol almost doubled with alcohol-related mortality more than from breast cancer, cervical cancer, and methicillin resistant staphylococcus aureus infection combined(23). In subsequent years where data are available, deaths related to both alcohol excess and alcoholic cirrhosis have plateaued, which reflects a stable level total population alcohol consumption over the previous decade(22). Nonetheless, population alcohol consumption continues to represent a significant burden to UK healthcare.

The most recent annual data released by the Office of National Statistics (ONS) regarding alcohol-related deaths (from 2013), revealed that alcohol was responsible for 8,416 deaths – equivalent to a standardised mortality rate of 14.0 deaths per 100,000 population(24). Alcohol-related deaths in the East Midlands were marginally higher than this standardised mortality rate estimate. Deaths were highest in the 60-64 year old age group for both genders. In the UK alcohol-related deaths predominate in males; 66% of deaths in the ONS 2013 data occurred in males, which closely parallels that both 67% of UK cirrhosis deaths occurring in male patients(19), and 61.9% of cirrhosis cases in UK males are due to alcoholic liver disease(11).

The majority of the UK population consume alcohol, albeit most moderately; 22% of the adult population in the UK currently abstain from alcohol, whilst 20-30% of the population consume 70-80% of the total alcohol(22). Overall, an estimated 7-8% of the UK population can be classified as alcohol dependent(25). Hazardous alcohol consumption continues to result in a significant cost to healthcare; 150,000 UK hospital admissions per year are due to alcohol(25), and up to one third of Accident and Emergency admissions may have alcohol causally linked. Whilst there are no formal cost analyses for liver related admission in the UK, costs of admissions or critical care units for alcohol liver disease in 2005 was estimated to cost the NHS £14.7million, and for liver transplantation £48,000 per quality adjusted life year (QALY) for patients with alcoholic liver disease(26).

Histology of Alcohol-Related Liver Disease

Simple alcohol-related fatty liver is usually asymptomatic and the liver parenchyma will return to normal within 4-6 weeks of alcohol abstinence(27). Continued alcohol use results in a spectrum of disease through steatosis, inflammation (steatohepatitis), and hepatic fibrosis, the latter occurring in 40-60% of hazardous alcohol users over 25 years(28). Cirrhosis occurs in 20-30% of lifelong heavy drinkers. Progressive fibrosis and cirrhosis are related to a number of phenotypic and environmental co-factors (including concurrent obesity or chronic viral hepatitis), and genetic co-factors which are yet to be fully established.

Alcoholic hepatitis is an acute inflammatory condition of the liver which can be superimposed upon any stage of alcoholic liver disease, although 90% of cases of severe alcoholic hepatitis occur in patients with established cirrhosis(29). Severe alcoholic hepatitis results in significant short term mortality. In a recent large randomised controlled trial of 1,053 patients assessing the effect of prednisolone and pentoxyfylline (a tumour necrosis α inhibitor), 28 day mortality in the placebo group was 17%, with no significant improvements in mortality in the three active treatment groups(30). At varying alcohol consumption thresholds, alcohol misuse is also strongly associated with the development of many cancers, hypertension and cardiovascular disease, chronic pancreatic and injuries and violence(31).

Impact of Alcohol Consumption Patterns

A large number of longitudinal studies have addressed how the quantity, frequency and type of alcohol consumed impacts development of

cirrhosis or mortality, often however with quite conflicting results. Recent NHS guidance advises that alcohol consumption in men and women should not regularly exceed 2-3 units daily, and 14 units per week in total(32) (in the United Kingdom a standard alcohol unit is defined as 8 grams of pure ethanol). Nonetheless, two recently reported longitudinal studies from the UK suggest that alcohol consumption around these recommended safe drinking limits still carries a significant risk of cirrhosis development and complications.

The first study, a long term follow up of 9,722 male workers from two cohorts in Scotland over a median of 29 years, showed that risk of liver disease-related mortality was significantly increased at a weekly alcohol consumption of 15-21 units (HR 5.61, 95% CI 2.54-12.4), with further increases above this weekly consumption threshold(33). The second study, data reported from the Million Women study of 1.3 million women recruited through UK breast cancer screening, showed increased risk of cirrhosis development or hospitalisation at 7-15 units per week alcohol consumption in all studied BMI categories(34). Importantly, both studies highlighted the important synergism between alcohol consumption levels and obesity in increasing adverse outcomes with greater hazard ratios than individual risk factors alone.

With increasing alcohol consumption, the risk of adverse health outcomes increases exponentially. A metaanalysis of 9 longitudinal studies totalling 2,202 cases of chronic liver disease showed the relative risk of developing cirrhosis is 2.90 with 25 grams of ethanol per day (approximately) but rises markedly to 7.13 with 50 grams (6.25 units) per day ethanol

consumption and 26.52 with 100 grams (12.5 units) of daily ethanol consumed(31). In this metaanalysis there was a clear dose response relationship between alcohol consumption and risk of cirrhosis development, although this relationship is controversial. A more recent metaanalysis of 17 studies examined this effect further by analysing the risk of morbidity (cirrhosis development) and mortality separately for men and women. In women, there was a clear dose response relationship between alcohol consumption and risk of death, whilst for men a threshold effect for mortality at 12-24 grams (1.5-3 units) of daily ethanol was observed, below which there was no dose response. Furthermore, an increased risk of cirrhosis development was only observed in daily alcohol consumption groups of above 24-36 grams (3-4.5 units) of ethanol in women and above 36-48 grams (4.5-6 units) of ethanol in men respectively(35).

Whether drinking frequency (in terms of either days per week consuming alcohol, or binge drinking (consumption of excessive alcohol in a short time e.g. one to two days per week) versus regular alcohol consumption) impacts upon health outcomes is more controversial still, with a number of studies drawing contrasting conclusions(36-39). Importantly, these prior studies are confounded by abstinent patients (who are the comparator group) consisting of both lifelong abstainers but also ‘current abstainers’. The latter are in some cases likely to have been prior harmful alcohol consumers who stop drinking due to symptom development. Thus the effect of alcohol consumption is underestimated in the other studied groups. Subsequently, a more recent study by Askgaard assessed drinking

amount and frequency in 55,917 Danish participants compared to lifetime abstainers only. Although daily alcohol consumption was associated with an increased risk of developing cirrhosis compared to less frequent drinkers, it is likely that this effect was explained at least partially by reduced net weekly alcohol consumption in the lower frequency groups(40). Lastly, a higher proportion of wine consumption as part of an individual's total alcohol intake has been observed to be associated with reduced cirrhosis risk compared to consumption of beer or spirits(40, 41).

Alcohol-Related Liver Disease Mortality

Survival in patients with advanced alcoholic liver disease is poor, with a range of 5 year survival rates in primary studies of hospital based cohorts of 43-63%(42-44). Consistently in these longitudinal studies, alcohol abstinence is by far the greatest predictor of future mortality. A recently published metaanalysis of 7 cirrhosis cohort studies indicated that alcohol abstainers retained a survival advantage at all future time points after 18 months compared to continued drinkers. This remained true in subgroup analyses of both compensated and decompensated cirrhosis(45). Unfortunately, as described in further detail later in this thesis, the majority of patients with alcohol dependence do not achieve abstinence(28).

The only currently available treatment for advanced cirrhosis is liver transplantation. The UK performs approximately 600-700 liver transplants per year at a cost of more than £50,000 each. Alcoholic liver disease is the second most common indication for transplantation in the developed world(46). The rising burden of alcohol use and related liver disease, and the

move towards transplantation even without a period of alcohol abstinence(47), will further increase the burden on health services and transplant allocation (there is already a severe nationwide organ shortage for liver transplantation). A combination of shifting paradigm towards alcohol moderation and abstinence at a population level, and utilising newer investigative tools to identify earlier reversible stages of liver disease in the community will be necessary to reverse these concerning trends.

Non-Alcoholic Fatty Liver Disease

Non-alcoholic fatty liver disease (NAFLD) is defined by hepatic steatosis in the absence of secondary causes of hepatic fat accumulation, including hazardous alcohol consumption, medications or metabolic disorders such as abetalipoproteinaemia. It is usually seen in association with risk factors for the metabolic syndrome(48). NAFLD encompasses a disease spectrum of simple fatty liver (simple steatosis), inflammation with fatty liver (non-alcoholic steatohepatitis) (NASH)), hepatic fibrosis and ultimately cirrhosis.

The main pathological mechanism for the development of NAFLD is insulin resistance, and this explains the intimate link to obesity, type 2 diabetes and other metabolic risk factors. Indeed both obesity and type 2 diabetes infer a more aggressive NAFLD timeline, a combination of increased hepatic fat delivery, de novo lipogenesis and proinflammatory cytokine upregulation contributing to oxidative stress and subsequent inflammation and scarring(49-51). Previous screening studies have observed a significant prevalence of NAFLD in the general population, including 30%

prevalence in Germany as detected by hepatic ultrasound(52), and 31% and 29% prevalence in the US and Hong Kong respectively detected by magnetic resonance spectroscopy(53, 54). Steatosis prevalence is greater in men than women, and varies by ethnic group with increased prevalence observed in Hispanics compared to white or black patients(53).

NAFLD prevalence continues to increase significantly. Two recent UK general practice studies have shown that NAFLD is the most common diagnosis amongst patients with elevated liver enzyme levels(55, 56). Of particular note, NAFLD accounted for 4 fold more diagnosed cases than alcoholic liver disease (43% of elevated LFT cases were due to NAFLD versus 10% ALD) in a study of 3 London boroughs(55). Recent data from the CPRD showed that 25% of cirrhosis cases in the UK are due to cryptogenic cirrhosis (of whom the vast majority will be NAFLD), with a 1.7 fold increase in incidence in men and 2.5 fold increase in incidence in women between 1997 and 2010. Given current population trends of obesity, the health burden attributable to NAFLD is likely to worsen still. In the US, where the obesity crisis is more advanced than the UK, a general population study showed a doubling of NAFLD prevalence between 1988 and 2008(57). Subsequently, NAFLD has now overtaken alcoholic liver disease as the second leading indication for liver transplantation in the US(58). Even childhood NAFLD is increasingly recognised – in previous studies 3% of children aged 4-12 years had NAFLD(59), rising to as high has 53% in obese children(60).

NAFLD Risk Factors

The majority of NAFLD cases are related to risk factors for metabolic syndrome, most notably increased body mass index and type 2 diabetes, both of which are increasing in the general population due to poor dietary choices and physical inactivity. Hospital episode statistics (HES) data published in 2014 revealed a marked increase in obesity prevalence in the UK - in the previous decade obesity prevalence has risen from 13.2% to 24.4% in men and 16.4% to 25.1% in women(61). Moreover, the prevalence of overweight and obesity has also risen significantly to 66.6% in men and 57.2% in women, and mean population BMI is 27. The majority of the UK population therefore has a risk factor for the development of NAFLD.

As body mass index rises, the risk of NAFLD presence, NASH and hepatic fibrosis also increase. In an autopsy study of 351 recently deceased individuals, markedly obese patients (defined in this case as greater than 40% above ideal weight) had a 18.5% prevalence of NASH compared to 2.7% in lean patients, whilst hepatic fibrosis prevalence was doubled in the obese (13.8% vs. 6.6%)(62). Furthermore, NAFLD is almost universal in the morbidly obese. A metaanalysis of 12 studies totalling 1,620 patients with severe obesity undergoing bariatric surgery revealed NAFLD prevalence of 91%, NASH prevalence of 37%, hepatic fibrosis prevalence of 60% and a further 1.7% had previously undetected cirrhosis(63).

In parallel with rising obesity levels, the prevalence of type 2 diabetes has also continued to rise. The most recent estimates in the UK (from Quality and Outcomes Framework data in 2013) showed total diabetes prevalence of

6% (3.2 million people), of whom 90% are patients with type 2 diabetes(64). Importantly, many cases of type 2 diabetes and impaired fasting glucose remain undiagnosed. A general population based study of 11,247 randomly selected adults in Australia invited to undergo an oral glucose tolerance test doubled the known type 2 diabetes prevalence to 7.4%, and a further 5.8% had previously undetected impaired fasting glucose(65).

Type 2 diabetes prevalence is likely to increase significantly in upcoming decades and worldwide diabetes prevalence is forecast to double since 1995 levels to 300 million people by 2025(66). This will subsequently make a significant contribution to the worsening NAFLD epidemic. NAFLD prevalence is greatly increased in patients with type 2 diabetes, with ranges 48-70% of patients with type 2 diabetes also having NAFLD observed in prior studies(67, 68), The presence of diabetes in NAFLD patients significantly predicts fibrosis development and progression(69, 70) and development of hepatocellular carcinoma(71, 72), even in patients with minimal background liver fibrosis(73). Furthermore, type 2 diabetes is an independent risk factor for death due to cirrhosis. De Marco et al reported a large population-based study in Verona, Italy where 7,148 patients with type 2 diabetes were identified from a variety of healthcare databases and longitudinally followed for 5 years. Compared to the background Verona population, identified patients with type 2 diabetes had a 2.5 fold increased risk of death due to cirrhosis, with greatest risk observed in those taking oral hypoglycaemic agents or insulin (standardized mortality ratios 4.9 and 6.8 respectively; likely

to be a surrogate marker of both exposure time to diabetes and adequacy of diabetes control)(74).

NAFLD Longitudinal Outcomes

Further to risk factors for presence and progression of NAFLD, determining the stage of NAFLD is important in predicting relevant longitudinal outcomes. Table 1 shows pooled data from longitudinal NAFLD cohorts with more than 5 years of follow up, adapted from an editorial published in 2010(75).

Table 1: Longitudinal data from NAFLD natural history studies of greater than 5 years follow up (adapted from Angulo et al(75))

Diagnosis	n	Cirrhosis prevalence n	Liver related deaths n	Overall deaths n	Follow up (years)
Simple Steatosis	342	2 (0.7%)	3 (0.9%)	111 (32.5%)	15.6
NAFLD	798	40 (6%)	30 (3.8%)	204(25.6%)	15.2
Non-alcoholic Steatohepatitis	205	16 (10.8%)	15 (7.3%)	83 (40.5%)	15.5
Cirrhosis	252	-----	46 (18.3%)	62 (24.6%)	10.25

n given as patient number (percentage); NAFLD = non-alcoholic fatty liver disease. Liver related deaths refer to deaths directly contributed to by hepatic decompensation or hepatocellular carcinoma as defined in the individual studies.

Simple steatosis (hepatic fat accumulation in the absence of steatohepatitis) is associated with a relatively benign course, with overall fewer than 1% of patients developing cirrhosis over a median 15 year follow up(76-78). Comparatively, studies observing patients with NASH and/or hepatic fibrosis showed a more than ten-fold increased risk of developing cirrhosis (76, 79, 80), and a more than sevenfold increased risk of liver-

related death over a similar follow-up period. Nonetheless, fibrosis progression in NAFLD is overall a relatively slow process. A recently published metaanalysis of 11 studies of NAFLD patients who underwent paired liver biopsies more than one year apart quantified fibrosis progression as 0.14 fibrosis stages per year for NASH patients and 0.07 fibrosis stages per year for patients with simple steatosis(81). Fibrosis progression was associated with hypertension and low AST:ALT ratio levels on metaanalysis, although type 2 diabetes has been found to be associated with progressive or advanced fibrosis in several individual studies(69, 70, 82). However, mean fibrosis progression may be as high as 0.29 fibrosis stages per year in patients with the most rapid fibrosis progression(82). It is important to note that these reported studies are open to significant spectrum bias, as these are from secondary and tertiary care hospital populations with high risk features for fibrosis progression e.g. failure to engage in lifestyle changes, and so these progression rates are likely to be an overestimate.

Whether NAFLD is independently associated with an increased risk of all-cause mortality is more controversial. Several studies have shown an increased risk of mortality in patients with NAFLD(67, 80, 83, 84), however these cohorts have been derived from patients either with raised transaminases or recent hospital admission, and therefore represent those NAFLD patients likely to be most at risk of adverse events. Indeed, Kim et al's general population study using the 3rd US National Health and Nutrition Examination Survey (NHANES3), which represents the least selected study population as NAFLD patients were identified from the general population

with ultrasound evidence of steatosis, revealed that NAFLD patients were no more likely to die during follow up than the general population (HR 1.05, 95%CI 0.93-1.19).

Where studies have stratified the population based upon NAFLD severity however, an increased risk of mortality associated with more advanced NAFLD stages becomes apparent. Longitudinal studies which have analysed patients with simple steatosis and NASH separately have observed that increased mortality rate in NAFLD can be attributed to higher mortality in the NASH group alone(76, 80). More recent studies have assessed the risk attributable to hepatic fibrosis within NASH, and demonstrated an increased risk of liver-related outcomes and all-cause mortality in patients with advanced fibrosis (stage 3 or greater) rather than NASH or earlier fibrosis stages(85-87). Identifying NASH patients with fibrosis is clearly important in determining those patients mostly at risk of adverse outcomes, who might benefit most from aggressive lifestyle modification or medical interventions to improve their NASH and fibrosis.

Whilst a diagnosis of NAFLD understandably increases the risk of liver disease and liver-related death, numerous studies have shown a striking association between NAFLD and subclinical markers of cardiovascular disease, prevalent cardiovascular disease and cardiovascular deaths. NASH in particular shares key pathophysiological features with atherosclerosis including increased oxidative stress and inflammatory cytokines and reduced adiponectin levels(88). A recently published systematic review of 27 studies concluded that there was significant evidence of NAFLD association with

subclinical markers of cardiovascular disease (including endothelial dysfunction, coronary calcification and carotid intima-media thickness)(89), although whether the association is explained purely by shared risk factors of the metabolic syndrome is controversial. Interestingly Targher et al have shown in studies of their large clinic patient populations, that the presence of NAFLD in patients with type 1 or type 2 diabetes infers a significantly increased prevalence of both subclinical atherosclerosis markers, and overt cardiovascular disease development independent of metabolic syndrome parameters(68, 90). These findings appear to translate into an increased risk of cardiovascular death in patients with NAFLD. In the previously mentioned NAFLD longitudinal studies, cardiovascular disease is commonly the leading cause of death (accounting for 15-30% of all-cause mortality, compared to as low as 1.7% for liver-related deaths)(67, 76, 80, 84).

More recent studies have shown that the increased risk of cardiovascular death appears most profound in patients with advanced fibrosis defined by histological stage(87) or serum liver fibrosis markers(85). It is worth noting that lifestyle related treatments for NAFLD should improve both cardiovascular and hepatic risk. Weight loss of 5-10% from baseline (a typically suggested target weight loss to prevent fibrosis progression upon diagnosis of NAFLD) through dietary change and/or increased exercise significantly improves cardiovascular risk factors, protective cytokines such as adiponectin, and liver histology (91-94) (both steatosis and inflammatory constituents). Therefore it appears that stratification of liver disease also stratifies future cardiovascular risk. Early identification and treatment of

NAFLD is therefore likely to have profound effects on cardiovascular and liver-related mortality if adopted by patients.

Limitations of Traditional Liver Investigation Algorithms in Primary Care

Liver Function Tests

The algorithm for abnormal liver function enzymes currently utilised in Nottinghamshire is provided in Appendix A for reference. Traditionally, referral for investigation of suspected liver disease has been prompted by an abnormality in liver biochemistry, commonly called liver function tests (LFT), the main diagnostic modality for liver disease in primary care. Of the commonly reported liver enzymes, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are markers released in response to liver cell damage, whilst alkaline phosphatase (ALP) is a marker of cholestasis.

Previous estimates have shown that between 22% and 32% of patients in primary care will have liver function blood tests performed for chronic disease screening or as a result of systemic symptoms, of which 15-22% will be abnormal(55, 95). Raised transaminase levels are associated with an increased risk of future liver disease diagnoses and liver-related mortality(95, 96), whilst transaminase levels seem to have a J-shaped relationship with future all-cause mortality(96, 97). A recently reported survey of 352 gastroenterologists from France, suggested that abnormalities in liver enzymes still have a significant impact on the decision to perform liver biopsy(98, 99). However, it is becoming increasingly recognised that liver

function tests do not reflect the function of the liver nor severity of liver pathology accurately, and their utilisation is therefore a poor strategy for identifying liver disease.

Poor specificity of liver function enzymes has been demonstrated in both primary and secondary care studies. In a Nottingham hospital-based study by Skelly et al which reported 354 patients who underwent liver biopsy for persistently raised liver enzymes, only 26% patients had evidence of hepatic fibrosis. Moreover, the positive predictive value of raised ALT for predicting fibrosis was only 18%, and for raised gamma glutamyl-transpeptidase (GGT) was only 11%. A large retrospective study of primary care patients in Tayside, Scotland reported patients who underwent liver function tests over a 15 year period between 1989 and 2003(95). Only 1.14% of patients with an abnormal liver function test were diagnosed with liver disease during follow-up, whilst the positive predictive value for raised transaminases for predicting the development of liver disease was only 3.9% at 5 years. Moreover, in a further prospective study of 1118 patients with abnormal liver function tests from primary care practices in Birmingham and Lambeth(56), no explanation for test abnormality was found in 45% of patients, and 20% of patient's ALT levels normalised upon repeat testing. This poor test specificity results in many patients undergoing invasive investigations such as liver biopsy without having clinically significant liver disease.

In addition, many studies have demonstrated the poor sensitivity of liver function enzymes for detecting hepatic fibrosis, which is most striking in

studies of patients with non-alcoholic fatty liver disease (NAFLD). General population studies have shown that the majority of people with NAFLD have normal transaminase levels(53, 97, 100, 101), including as many as 88% of patients with any NAFLD(97) and 92% of patients with NASH(100). Several secondary care studies have evaluated the histological findings of their NAFLD patients with normal ALT who underwent liver biopsy. It has been clearly demonstrated that patients with normal ALT can still have the full histological spectrum of NAFLD including cirrhosis(102, 103). In studies which have compared NAFLD patients with normal and abnormal ALT levels, there were no significant differences in the prevalence of NASH, significant fibrosis or cirrhosis(102-106). Furthermore, liver enzyme levels commonly regress to normal during advanced disease progression(107-109).

In an effort to improve the sensitivity of ALT for the detection of liver disease, work by Prati et al in a large study of 6,835 first time blood donors defined alternative abnormal values for ALT of >19IU/L for women and >30IU/L for men based upon the 95th percentile of values in the studied population(110). However, in a study of 233 obese women undergoing liver biopsy at the time of laparoscopic gastric bypass, Kunde et al subsequently showed that cases reclassified as abnormal by Prati's cutoffs were mostly simple fatty liver disease only, and the sensitivity for NASH detection remained inadequate at 74%(111).

Abdominal Ultrasound

Abdominal ultrasound is a common test requested in primary care as part of the workup for patients with elevated liver enzymes. Ultrasound may

yield a number of potential causes for elevated liver enzymes, including detection of masses or choledocholithiasis as a cause for cholestasis, identification of fatty liver disease and identification of features of cirrhosis (e.g. nodular appearance to the hepatic parenchyma) or portal hypertension (e.g. splenomegaly or reversal of portal venous flow). Whilst a positive finding on ultrasound is highly specific, and therefore useful for stratifying patients most at need of specialist hepatology advice, the sensitivity of ultrasound for detecting either steatosis or fibrosis is inadequate.

Hepatic steatosis causes increased echogenicity in the liver, such that on ultrasound the liver parenchyma appears brighter than the ipsilateral kidney(112). Compared to liver biopsy (considered the gold standard for quantification of hepatic steatosis(113)), the sensitivity for ultrasound detecting any steatosis is only approximately 60-65%(114, 115). This sensitivity improves with rising steatosis threshold levels(100, 115, 116), but is reduced in patients with morbid obesity(117). When considering grading of steatosis (into categories of mild, moderate and severe), the sensitivity of ultrasound is poorer still, being as low as 11%(118). It is unrealistic, therefore, to reliably use ultrasound as a longitudinal indicator of improving steatosis.

Similarly, ultrasound has a poor sensitivity for detecting hepatic fibrosis and cirrhosis. Although nodularity of the liver on ultrasound is a high specificity finding for cirrhosis, its sensitivity is poor at only 53-54%(119, 120). It is important therefore that the absence of steatosis or cirrhosis on ultrasound does not falsely reassure primary care doctors that liver disease is not present.

Liver Biopsy

Subsequently, referral into secondary care for investigation of suspected liver disease is most commonly to determine the disease aetiology and liver fibrosis stage associated with abnormalities in liver function enzymes. Currently, the gold standard investigation for further evaluation of these features in secondary care is liver biopsy. Liver biopsy can be performed either percutaneously by passing a needle between the lower right hand side ribs, or via the transjugular route; both result in an approximate 1 in 50,000th section of liver tissue being obtained(121). There are a number of limitations to the liver biopsy procedure.

Firstly, liver biopsy is invasive and not without potentially significant complications. Data from the NHS between 1998 and 2005 of 61,187 people who underwent liver biopsy showed major haemorrhage post liver biopsy of 6 cases per 1,000 liver biopsies, whilst death directly related to liver biopsy was observed in 1 in 10,000(122). Furthermore, in a large retrospective case study of 4,275 percutaneous liver biopsies performed between 1994 and 2002 in Canada, Myers et al reported significant complications in 32 patients (0.75% of biopsies) whom required further hospitalisation(123). The commonest indications for admission were pain (0.5%) and bleeding (0.35%). Death secondary to liver biopsy occurred in 0.14%, albeit all deaths occurred in patients who were high risk due to malignancy. Similarly, in a retrospective report of 68,726 percutaneous liver biopsies performed in the Netherlands, death occurred only in patients with malignancy or cirrhosis, and was due to haemoperitoneum in all cases(124). The use of ultrasound guided liver

biopsy(121), or transjugular liver biopsy(125) is associated with a slight reduction in procedural complications. Transjugular biopsy has the added benefit of prognostic information gained from measurement of the hepatic venous pressure gradient (HVPG), although this is only available typically in specialist hepatology centres. Biopsy samples via the transjugular route tend to be smaller and more fragmented than those via the traditional percutaneous route(126).

Secondly, liver biopsy is a specialist procedure requiring performance by a radiologist or gastroenterologist. Although it is a day case procedure, a period of observation (usually 4-6 hours) is required in hospital to detect early complications from the biopsy process. The cost to the NHS for each liver biopsy is therefore substantial, and estimated to be £546.02 per procedure in recent NHS reference costings.

Thirdly, liver biopsy is not a 100% accurate gold standard investigation and a significant amount of fibrosis stage misclassification is associated with the procedure. In studies where patients have undergone sequential liver biopsies on the same day, discordance of fibrosis staging has been estimated at 30-55%(127-129), although is less pronounced if large biopsy samples more than 25mm in length are obtained(129).

As a result of these shortcomings, there has been intense research in recent years to find non-invasive alternatives which are accurate enough to avoid the need for liver biopsy in a substantial number of patients.

Justification of Altering Liver Disease Investigation in Primary Care

As already described, the current model of liver disease investigation is inadequate. It results in a significant number of liver disease cases being identified late when patients have symptoms of liver failure, which is subsequently a contributing factor to high cirrhosis incidence and mortality in the United Kingdom. These factors underpin the rationale that an alternative approach to liver disease detection in primary care is required. Understandably, liver biopsy cannot be suggested as a first line investigation due to its cost and risk of significant complications.

As patients who develop ALD and NAFLD have defined identifiable risk factors for progressive liver disease, a possible alternative approach is to target investigations at these individuals using newer non-invasive liver fibrosis tests. Identifying non-invasive alternatives to liver biopsy for the detection of hepatic fibrosis has become an area of intense research in recent years. A large number of laboratory panel and imaging liver biomarkers have been validated in secondary care populations to more accurately stratify liver fibrosis and cirrhosis than traditional liver function tests(130), and these encompass all major causes of chronic liver disease. Many of these are serum or imaging investigations which would be feasible to use in a primary care setting to improve the detection of liver disease.

In addition to preventing cirrhosis and related deaths from earlier liver disease detection, a potential benefit to utilising these newer tests is to improve the cost effectiveness of liver disease investigation. The investigation of liver disease in specialist centres can be both expensive for

the healthcare system and inconvenient to the patient. Recent economic modelling from York has suggested that the substitution of elastography (an imaging test which maps the elastic properties of tissue) for liver biopsy in a hospital setting would save £520 per patient investigated(131). Implementing these services in the community is likely to improve the health economic benefits of early liver disease detection yet further.

A further potential benefit of earlier liver disease detection is that it is likely to result in increased uptake of lifestyle-related interventions, for which there is evidence of fibrosis regression. Brief intervention advice for hazardous alcohol use is effective, with metaanalysis estimates of numbers needed to treat of 8-10 to significantly reduce alcohol intake(132, 133). There is good evidence that screening for alcohol use alone results in reduction of future reported alcohol consumption(134, 135) and that simple interventions such as leaflet-based information are as effective as more formal structured face-to-face appointments(136). Furthermore, a metaanalysis of 32 studies assessing 7,521 subjects suggested that compared to control groups, Brief Intervention advice is associated with a reduction in mortality (HR 0.57; 95% CI 0.38-0.84)(137). For NAFLD, weight loss via dietary intervention, increased physical activity or a combination of both is the mainstay of early management and has been extensively studied. Target weight loss of 7-10% appears to be the threshold at which significant histological improvements, including improvement in steatosis, inflammation and fibrosis occur(92, 94). Importantly, the infrastructure for performing such lifestyle interventions is

already well established in primary care, and could be delivered in parallel with new primary care pathways for investigating chronic liver disease.

The Wilson and Jungner criteria (138) and more recent Government national screening criteria (139) provide a set of 10 and 20 recommended standards respectively which should be met before the initiation of national screening programmes. In particular these define the importance of the target condition, the suitability of candidate investigations for detecting the condition in the general population and considerations of the impact of screening the population with particular note to false negative or false positive results. As discussed in this introduction, there are factors regarding liver disease screening which are known (natural history of the disease, latent presymptomatic phase, importance of the health problem to the UK and accepted treatments). However, other factors require further study before large scale screening for chronic liver disease can be considered. These include determining in a primary care setting the prevalence of liver disease within specific risk factor groups which might facilitate targeted screening, the acceptability of newer non-invasive liver disease investigations, validation of these investigations in primary care, the cost of case finding and the need for longitudinal, rather than just cross-sectional, case identification.

Aims of Thesis:

With these above factors borne in mind, clearly further research is required to determine the validity of screening investigations for liver disease in primary care, and determining the optimal approach for doing so.

Subsequently, the body of work within this thesis has the following aims in order to further the research into non-invasive liver disease stratification within a primary care setting:

a) To perform a systematic literature review of studies which have employed screening for ALD and NAFLD in a community setting and evaluate the diagnostic performance of non-invasive markers in this specific context.

b) To assess the feasibility of a community diagnostic pathway for detecting ALD and NAFLD within the United Kingdom healthcare system, and quantify the amount of significant liver disease that is detected using this approach.

c) To explore which risk factors and fibrosis biomarkers yield the highest prevalence of significant liver disease diagnoses.

d) To explore the patient perspectives of liver disease investigation of the pathway and get some preliminary insights into the uptake of subsequent lifestyle changes.

Chapter 2: The use of non-invasive biomarkers to stratify liver disease due to alcoholic and non-alcoholic fatty liver disease in a community setting: A Systematic Review

The introductory chapter of this thesis provided an overview of chronic liver disease epidemiology and current primary practice for investigating suspected liver disease. The chapter highlighted the rising incidence and mortality of cirrhosis, and the contributions of population level lifestyle choices and current investigation algorithms as key drivers of these adverse liver-related outcomes.

Numerous serum-based and imaging biomarkers have been investigated and validated in secondary care studies, and their satisfactory diagnostic accuracy for predicting fibrosis compared to liver biopsy as a gold standard demonstrated. The attraction of using these alternative investigations in a hospital setting includes avoiding the need for invasive tests to stage liver fibrosis such as liver biopsy, and additionally prognostic information of predicting those patients at increased risk of future liver-disease related adverse outcomes (86, 140, 141). In a primary care setting, these newer tests are likely to be more sensitive than liver function tests for detecting hepatic fibrosis and cirrhosis, thus providing an opportunity to intervene with lifestyle interventions to slow or even reverse fibrosis progression. A number of pilot studies have subsequently been performed evaluating non-invasive biomarkers in primary care or the community, but to date the information from these primary studies has not been collated or meaningful suggestions for clinical practice derived.

The following is a comprehensive narrative systematic review of prior studies which have used non-invasive biomarkers in the general population to stratify hepatic fibrosis and cirrhosis. The findings of this systematic review, in combination with relevant hospital studies where specific data are lacking, will be utilised to create an evidence based biomarker pathway to be studied and reported in the subsequent chapters of this thesis.

The aims of this systematic review are as follows:

i) to determine the prevalence of clinically significant liver disease (hepatic fibrosis or cirrhosis as defined by individual studies) detected in the studied populations.

ii) to evaluate the impact of index test selection, index test result threshold and liver disease risk factor selection in determining the prevalence of hepatic fibrosis and cirrhosis.

iii) to describe the diagnostic performance of studied fibrosis markers compared to the traditional gold standard investigation (liver biopsy).

iv) to determine the screening uptake of invited participants in the studied populations.

v) to identify the percentage of participants with hepatic fibrosis or cirrhosis but normal alanine aminotransferase (ALT) results, indicating disease which would be missed with traditional investigation algorithms.

Methodology

This systematic review was conducted according to guidance provided by the Cochrane Collaboration handbook for systematic review of interventions(142), and following a pre-specified, peer-reviewed protocol which is described below. The study identification, data collection and subsequent data analysis were performed in conjunction with a second researcher Dr. Rebecca Harris (RH; Clinical Research Fellow in Hepatology, Nottingham Digestive Diseases Biomedical Research Unit).

Search Strategy

A structured search algorithm was developed for identification of primary studies from a selection of electronic databases which was derived using the following PICO question structure:

Participants – Unselected adult patients, or adult patients with risk factors for alcoholic liver disease (ALD) or non-alcoholic fatty liver disease (NAFLD) in a general population setting

Intervention – Non-invasive biomarkers of liver fibrosis

Comparison – Liver biopsy (although studies were eligible for inclusion if reporting liver disease prevalence without liver biopsy validation as described below).

Outcome – Liver fibrosis or liver cirrhosis

Key search terms (including possible alternative spellings) and MeSH terms relevant to liver disease, index tests and the community setting were

defined by the investigators DH & RH. Subsequently, the electronic database search algorithm was derived in collaboration with an expert librarian (Alison Ashmore; University of Nottingham) with extensive experience in the performance of systematic reviews. Search strategies derived for the target condition, index tests and study location were defined consecutively, and then combined using the 'AND' command. Further methodological search filters (e.g. defining adult, time filters and English studies) were not used for the search strategy as these are likely to omit relevant studies with low precision(143, 144). The final search algorithms utilised for specific electronic databases, and citations identified at each search step, are listed in appendix B.

A previous study of the sensitivity of utilising specific electronic search databases in 8 previously published systematic reviews, showed that 6% of relevant studies are not identified by electronic search databases, whilst the single most sensitive electronic database (OVID Medline) identified only 79% of relevant studies(145). Therefore, in order to optimise the sensitivity of our own search algorithm, a combination of electronic databases and additional grey literature searches were utilised. Identification of relevant studies was commenced in November 2014 and completed in January 2015 using the following sources:

i) Electronic databases – OVID MEDLINE, OVID EMBRASE, Thomson Reuters Web of Science, Cochrane library, DARE (Database of Abstracts of Reviews of Effects), ProQuest thesis

ii) Hand searching of conference proceedings of major United Kingdom and worldwide conferences from 2010 to present - British Society of Gastroenterology, Digestive Disorders Federation, British Association for the Study of Liver Disease, European Association for the Study of Liver Disease, Digestive Diseases Week and American Association for the Study of Liver Disease conferences.

iii) Targeted search of reference lists of identified primary studies.

The literature search was performed independently by the 2 investigators (DH and RH), who screened titles and abstracts of all articles identified and excluded those with no relevance to the research question. The full text of all remaining articles was read in full to ensure that they met the study inclusion criteria.

Study Selection Criteria

Listed below are the criteria which were used to screen individual studies for eligibility for inclusion in the systematic review. Randomized-controlled trials, prospective cohort studies and case control studies were considered for inclusion if the following criteria were met:

1/ The study was performed exclusively in adult patients defined as aged 18 years or older.

2/ The study population was drawn from a non-secondary care setting e.g. primary care, the general population or outreach units.

3/ The study population underwent investigation using non-invasive index tests which would stratify the individual's risk of liver fibrosis.

4/ The prevalence of hepatic fibrosis or cirrhosis, as defined by the studied index test, was reported as an outcome measure in the study. Importantly, validation of the index test results by liver biopsy was not an absolute requirement for inclusion within the systematic review.

5/ Participants were either recruited from an unselected population within the study's geographic location or selected for investigation based upon participant age or defined risk factors for either alcoholic liver disease (ALD) or non-alcoholic fatty liver disease (NAFLD).

However, studies were excluded from the review if any of the following criteria were met:

1/ Studies where data were not adequately presented regarding the studied patient population (specifically confirmation that the study was performed in a community setting) or the diagnostic threshold of index test utilised to determine liver fibrosis or cirrhosis.

2/ Studies where patients were solely investigated due to non-ALD or non-NAFLD related chronic liver diseases e.g. chronic viral hepatitis (Hepatitis B and C), autoimmune liver disease or genetic liver diseases.

3/ Studies not published in English language.

Data Extraction

Data from studies which were accepted for inclusion within the systematic review were independently extracted by the two investigators (DH/RH) into a pre-defined Microsoft Word template and subsequently compared for accuracy. Any differences between the data sets were resolved by discussion and if disagreements persisted, a third investigator (Indra Neil Guha, primary PhD supervisor to DH and RH; ING) was consulted to make a final decision.

The following data were collected from each study:

1/ Study characteristics – first author, journal of publication, year of publication, country of origin and research location, study design, time length of study cohort recruitment, sample size and population screening uptake.

2/ Patient characteristics – patient age, gender, liver disease risk factors (including overall population alcohol consumption and metabolic syndrome risk factors).

3/ Study outcome characteristics – prevalence of hepatic fibrosis and cirrhosis in the study population, validation of index test findings with histology (liver biopsy), percentage of patients with diseased state and normal alanine aminotransferase (ALT) levels.

4/ Index test characteristics – investigation performed, its conduct and diagnostic cut-off(s) utilized. Where possible, the diagnostic performance of index tests compared to liver biopsy was calculated using commonly utilised

diagnostic statistics (sensitivity, specificity, positive and negative predictive values and diagnostic odds ratios).

Outcome Measures

The primary outcome measuring determining inclusion or exclusion within this systematic review is that studies report an estimated fibrosis or cirrhosis prevalence within the studied population. Hepatic fibrosis is a spectrum of disease divided into a number of categories by fibrosis classification. The most common classifications associated with ALD and NAFLD (the METAVIR(146) and Kleiner criteria(147)) separate fibrosis into 4 stages (F1-F4). Subsequently, common nomenclature for fibrosis stage is: ≥F1 stage = presence of any fibrosis, ≥F2 stage = significant liver fibrosis, ≥F3 stage = advanced liver fibrosis, and F4 alone representing cirrhosis. The current systematic review adopts this nomenclature for reported outcomes from individual studies. Importantly, where individual studies do not indicate which fibrosis stage the reported disease prevalence refers to, the systematic reports fibrosis prevalence as ≥F1 (any) fibrosis.

Results

Overall results of the search strategy are demonstrated in Figure 1. 813 citations were identified from the electronic database search, and a further 6 records from conference abstract proceedings and article reference lists. In total 779 records were excluded upon screening the titles and abstracts. Of the 40 full text articles assessed for eligibility, 22 were excluded. Thus 18 articles (16 full journal articles and 2 abstracts), were reported within the narrative systematic review. Transient elastography, an imaging test

based upon ultrasound which measures liver stiffness, was the only imaging biomarker studied and was utilised in 10 studies. The remaining index tests were all serum-based; NAFLD Fibrosis Score (used in 5 studies), Fibrotest (3 studies), AST:ALT ratio (2 studies), APRI (2 studies), FIB4 (2 studies), BARD score (2 studies), BAAT score (2 studies), hyaluronic acid (1 study), Enhanced Liver Fibrosis Score (ELF score) (1 study) and the Southampton Traffic Light test (1 study). The baseline characteristics of individual studies and participants are displayed in Table 2, whilst the parameters of the serum-based biomarkers are listed at the foot of Table 2.

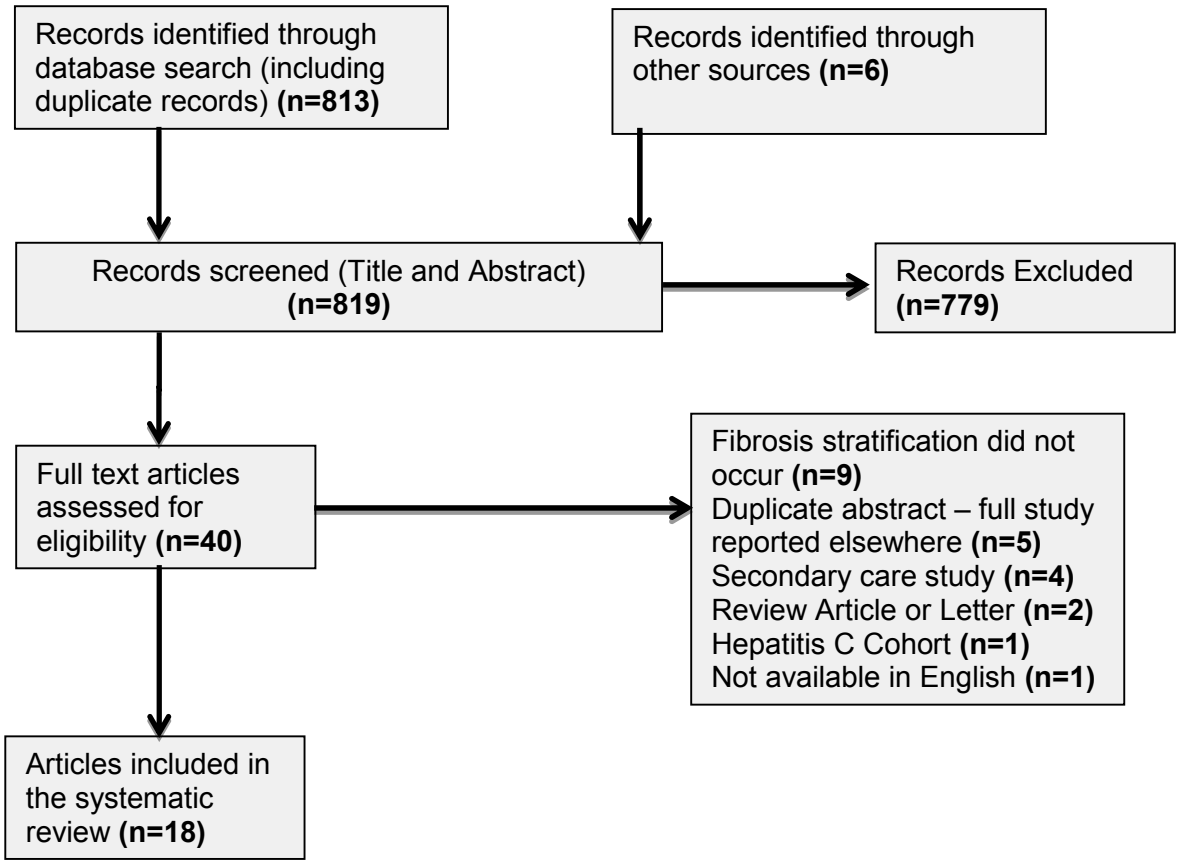


Figure 1. Flow diagram of the article search strategy and selection of studies eligible for data analysis

Table 2. Characteristics of 18 studies included within the systematic review, listed in order of risk factor investigated (unselected population, hazardous alcohol use and NAFLD risk factors)							
Study First Author	**Study Location/Patient Selection**	**Liver Disease Risk Factor**	**Index Test Utilised**	**Total Study Population**	**No. of Participants Screened**	**Mean Patient Age (years)**	**Male Gender (%)**
Baba(148)	Japan; annual medical checkup at community health centre	Unselected; alcohol and NAFLD subgroup analyses	TE	Not Stated	423 (of whom valid TE in 416 (98.3%)); subgroups of alcohol misuse (n=151) and NAFLD (n=58)	47.4	60.1%
Wong(54)	Hong Kong; subjects invited at random aged 18-70 from census database	Unselected. Subgroup analysis of patients with NAFLD (on MRS)	TE (all); NAFLD – AST:ALT ratio, APRI, BARD, FIB4, NAFLD fibrosis score	3000	922 (of whom valid TE in 759 (82.3%)) NAFLD subgroup - 264	48.0	42.2%
You(149)	South Korea; healthy subjects attending health check at local hospital	Unselected	TE	Not Stated	164 (of whom valid TE in 159 (97%))	56.0	54.7%
Lemoine(150)	The Gambia; community screening of healthy subjects	Unselected	TE	Not Stated	76 (of whom valid TE in 72 (94.7%)	49.5	43%
Malik(151)	United Kingdom; subjects recruited via advert and reviewed in private clinic	Unselected	TE	Not Stated	116	Not stated	Not stated
Fabrellas(152)	Spain; subjects invited at random from state health registry	Age 18-70 years	TE	Not Stated	502 (0f whom valid TE in 495 (98.6%)	47.2	41%

Zelber-Sagi(153)	Israel; random sample of participants of First Israeli National Health and Nutrition Survey	Age 25-64	Fibrotest	799	349 (of whom 338 (96.8%) had valid Fibrotest results)	50.8	54.7%
Poynard(154)	France; free medical check-up at community health centre	Age≥40 years	Fibrotest, TE	Not Stated	7,554 (of whom valid Fibrotest/absence of previous liver disease in 7,482 (99%)	56.9	55.1%
Roulot(155)	France; free medical check-up at community health centre	Age>45 years	TE	Not Stated	1,358 (of whom valid TE in 1,190 (87.6%))	57.7	60.5%
Veysey(156)	Australia; general population screening of elderly patients	Age ≥65 years	NAFLD Fibrosis Score	Not Stated	440; subgroup of 190 subjects with NAFLD (Fatty Liver Index)	78.0	40%
Sheron(157)	United Kingdom; screening of subjects from 9 primary care practices	Alcohol (AUDIT score ≥8)	Southampton Traffic Light Test	1,128	393	44.1	58.3%
Moessner(158)	Denmark; screening of subjects attending drug and alcohol outreach centre	Alcohol misusers who were HCV negative	TE	759	175	Not Stated	Not Stated
Armstrong(56)	United Kingdom; screening of subjects with raised ALT level from 8 primary care practices	NAFLD (ultrasound) and raised ALT	NAFLD Fibrosis Score (NFS)	Not Stated	295 (of whom NFS measured in 236 with available serum)	58.0	56.6%
Kim(85)	United States; subjects from NHANES3 general population cohort	NAFLD (ultrasound)	NAFLD Fibrosis Score	Not Stated	4,083	45.5	50.4%

	(1988-1994)						
Grattagliano(159)	Italy; subjects from 10 primary care practices	NAFLD (ultrasound)	Fibrotest	Not Stated	259	51.0	63.7%
Williamson(160)	Scotland; subjects from Lothian Type 2 Diabetes cohort (aged 60-74)	Type 2 Diabetes	Hyaluronic acid, BAAT, BARD, NAFLD fibrosis Score	5,454	939 (year 1 clinic attendees); subgroup of 663 with possible NAFLD	68.9	52%
Morling(161)	Scotland; subjects from Lothian Type 2 Diabetes cohort (aged 60-74)	Type 2 Diabetes; Subgroup analysis of patients with NAFLD (Ultrasound)	TE, ELF Score,	5,454	767 (year 4 clinic attendees); subgroup of 282 with NAFLD	71.4	52.8%
Das(162)	India; 1 in 3 sample of voting registry invited at random. Investigations both in	NAFLD (Ultrasound and CT) and raised ALT	TE	2,406	44 (out of 1,911 screened for NAFLD, 164 were positive and 44 also had raised ALT)	39.0	54%

ALT = alanine aminotransferase; AST = aspartame aminotransferase; APRI = AST:platelet count ratio; BAAT = score of age≥50 years (1 point), body mass index≥28 (1 point), ALT≥2 times upper limit of normal, triglycerides≥1.7mmol/L; BARD = weighted score of Body mass index ≥28 (1 point), AST:ALT ratio≥0.8 (2 points), Type 2 Diabetes (1 point); ELF = Enhanced Liver Fibrosis (combination of hyaluronic acid, TIMP metallopeptidase inhibitor 1 and Procollagen III N-Terminal Propeptide);FIB4 = combination of age, ALT, AST and platelet count; Fibrotest = combination of α2-macroglobulin,age, Apolipoprotein A1, bilirubin, gender, GGT and haptoglobin; MRS = magnetic resonance spectroscopy; NFS = NAFLD Fibrosis Score (combination of age, hyperglycemia, body mass index, platelet count, albumin, and AST:ALT ratio); Southampton Traffic Light Test = combination of hyaluronic acid, Procollagen III N-Terminal Propeptide and platelet count; TE = Transient Elastography

Study Uptake

Participant attendance for screening from the overall invited study population was displayed in 7 studies. Of these, 6 studies reported screening uptake for a single study visit whilst 1 study (Sheron et al (157)) reported uptake of a multiple step algorithm (see table 2). Of the studies reporting a single study visit, screening uptake ranged from 20% to 89%.

The lowest screening uptake occurred in the studies by Williamson(163) and Morling(161), in which 5,454 patients were randomly invited from the West Lothian type 2 diabetes registry, and 1,066 (20%) subsequently attended a baseline clinic visit. Subsequently, these studies report a year 1 clinic visit (939 attendees; 88% of study cohort) and year 4 clinic visit (767 attendees; 72% of study cohort), suggesting attrition of study cohort with multiple clinic visits.

Only the studies by Moessner(158) and Das(162) had a screening uptake of greater than 50%. In the study by Moessner, participants were opportunistically recruited from and investigated at a drug and alcohol outreach centre in Denmark, and therefore represented a somewhat captive audience. The study by Das is somewhat anomalous, as although similarly to other studies participants were invited at random from a larger database (in this case a 1:3 subsample of the Nagari Gram Panchayat village voting registry in India), a high screening uptake of 89% was achieved.

In the study by Sheron(157), subjects were initially screened for excessive alcohol use by the WHO AUDIT questionnaire which was sent by mail to patients of 9 primary care practices. Responses were received in

4630/9836 (47%) patients. Subsequently, only 393/1128 (34.8%) patients who had elevated AUDIT scores attended a clinic to undergo the index serum test, although it is likely that the true percentage of the population with excessive alcohol use screened is much lower than this due to the two step approach adopted.

Fibrosis Prevalence

All 18 studies included within the systematic review provided an estimate of liver fibrosis prevalence within the study population. Fibrosis prevalence in unselected or age-selected patients was reported in 10 studies, in 9 studies of patients with risk factors for NAFLD and 3 studies of patients with excessive alcohol use.

Of the studies with unselected or age-selected study populations, 8 studies provided an estimate of any liver fibrosis, 2 studies provided an estimate of significant liver fibrosis and 2 studies provided an estimate of advanced liver fibrosis (see Table 3). Reported liver fibrosis prevalence ranged from 0.7% to 25.7%. The lowest estimate, obtained in the study by Poynard(154), used a dual approach of investigating primarily with the serum test Fibrotest, and reinvestigating patients with a high result with TE. Subsequently only half of patients attended for reinvestigation, and so the reported fibrosis prevalence is likely to be an underestimate. Overall, prevalence of any fibrosis was 0-10% in 3 studies and >10% in the remaining 5 studies. In the 2 studies reporting significant liver fibrosis, prevalence estimates of 6.9% and 12.8% were obtained using TE≥7kPa and Fibrotest≥0.32 respectively. Estimates of advanced liver fibrosis were 0.9%

and 2.0%. With the exception of the study by You(149), in which type 2 diabetes prevalence was high at 11.9%, metabolic risk factors and alcohol consumption were in keeping with what would be expected in minimally selected general population studies.

Of the studies with patient populations investigated due to risk factors for NAFLD, 4 studies reported advanced fibrosis prevalence, 1 study reported significant fibrosis prevalence and 4 studies reported the prevalence of any liver fibrosis (see table 4). In the 5 studies reporting any liver fibrosis as an outcome measure, the prevalence ranged greatly from 0.8%-92.6%. The highest fibrosis prevalence estimates were reported in the studies of the West Lothian type 2 diabetes cohort by Williamson(160) and Morling(161). The high fibrosis estimates obtained in this study might be explained by the cohort being entirely made up of patients with type 2 diabetes who will have a high pre-test probability of liver fibrosis, selected index tests (e.g. BARD score) containing type 2 diabetes as a scoring parameter, and the very low fibrosis threshold used for FIB4 compared to previous studies. The studies by Baba(148) and Grattagliano(159), in which all patients had ultrasound evidence of NAFLD, provided estimates of fibrosis prevalence of 31% and 53.7% using TE and Fibrotest respectively. Significant fibrosis prevalence was only reported by Das(162); 15.9% of patients with NAFLD had a liver stiffness reading ≥8kPa whilst 1.4% of the entire study population were estimated to have significant liver fibrosis related to NAFLD. Estimates for advanced fibrosis ranged from 0-27.9% depending upon the study population and biomarker utilised. In all 4 studies, the investigated patients had already

the presence of NAFLD confirmed by ultrasound, magnetic resonance spectroscopy or fatty liver index. In the study by Wong(54), in which several index test values were reported, advanced fibrosis prevalence ranged from 0% (for NAFLD Fibrosis Score and APRI) to 12.1% for the AST:ALT ratio.

Of the studies reporting fibrosis prevalence due to ALD, 2 studies reported the prevalence of any hepatic fibrosis at 11% and 14.3%, and the third study reported the prevalence of significant liver fibrosis (≥F2 stage) of 17% (see table 5). The latter study by Moessner(158), was performed at an outreach centre of drug and alcohol misusers; the study population was therefore enriched with alcohol dependent patients which explains the high prevalence of significant liver fibrosis observed in this study.

Multivariate logistic regression analyses aiming to do identify factors independently associated abnormal biomarker results were reported in 5 studies (see table 6). The most commonly reported factors were obesity or elevated BMI (4 studies), patient age (3), male gender (2), ALT level (2) and waist circumference(2).

Table 3. Results of 10 studies reporting liver fibrosis prevalence in unselected patients or patients selected for age alone					
Study	**Risk Factor Prevalence**	**Outcome Measure**	**Index Test Threshold**	**Disease Prevalence**	**Normal ALT (%) (Diseased State)**
Baba(148)	BMI≥23 = 33.4% Alcohol >20g/day = 36%	Any liver fibrosis	TE (liver stiffness) ≥5.9 kPa	14.3%	55%
Wong(54)	Type 2 Diabetes = 5.2% BMI>=25 = 22.8%	Advanced Liver Fibrosis	TE (liver stiffness) ≥9.6kPa	2%	40%
You(149)	BMI>25 = 41.5% Type 2 Diabetes = 11.9% Hypertension = 25.2%	Significant Liver Fibrosis	TE (liver stiffness) ≥7kPa	6.9%	63.6%
Lemoine(150)	Not Stated	Any Liver Fibrosis	TE (liver stiffness) ≥7.2 kPa	11%	Not Stated
Malik(151)	Not Stated	Any Liver Fibrosis	TE (liver stiffness) ≥7kPa	19%	Not Stated
Fabrellas(152)	Hazardous alcohol consumption = 9%	Any Liver Fibrosis	TE (liver stiffness) ≥6.8kPa	5.7%	Not stated
Zelber-Sagi(153)	Type 2 Diabetes = 6.8% Hypertension 37.3% Metabolic syndrome = 18.6%	i) Any Liver Fibrosis ii) Significant Liver Fibrosis iii) Advanced Liver Fibrosis	i) Fibrotest ≥0.22 ii) Fibrotest ≥0.32 iii) Fibrotest ≥0.59	i) 25.7% ii) 12.8% iii) 0.9%	Not Stated
Poynard(154)	Hazardous alcohol = 22.5% BMI≥27 = 32.5% Dysglycaemia = 15.3%	i) Presumed Liver Fibrosis ii) Any Liver Fibrosis	i) Fibrotest>0.48 ii) Fibrotest>0.48 and TE (liver stiffness) ≥7.1kPa	i) 2.8% ii) 0.7%	i) 74.6% ii) 66%
Roulot(155)	Metabolic syndrome = 20.3% BMI≥30 = 17.1% BMI 25-29 = 45.8%	Any liver fibrosis	TE (liver stiffness) ≥8 kPa	7.5%	43%
Veysey(156)	NAFLD (fatty liver index>60) = 43.2%	Any Liver Fibrosis	NAFLD Fibrosis Score>0.676	18.9%	Not Stated

ALT = alanine aminotransferase; Fibrotest = combination of α2-macroglobulin, age, Apolipoprotein A1, bilirubin, gender, GGT and haptoglobin; kPa = kilopascals; NFS = NAFLD Fibrosis Score (combination of age, hyperglycemia, body mass index, platelet count, albumin, and AST:ALT ratio); TE = Transient Elastography

Table 4. Results of 9 studies reporting liver fibrosis prevalence in patients with risk factors for non-alcoholic fatty liver disease (NAFLD)					
Study	**Risk Factor Prevalence**	**Outcome Measure**	**Index Test Threshold**	**Disease Prevalence**	**Normal ALT (%) (Diseased State)**
Baba(148)	NAFLD (ultrasound) = 100%	Any liver fibrosis	TE (liver stiffness) ≥5.9 kPa	31.0%	Not Stated
Armstrong(56)	Type 2 Diabetes = 38.6% Obesity = 60.3%	Advanced Liver Fibrosis	NAFLD Fibrosis Score ≥0.676	7.6%	N/A (subjects selected due to abnormal LFTs))
Kim(85)	NAFLD (detected on ultrasound) = 100% Type 2 Diabetes = 8.4%	Liver Fibrosis	NAFLD Fibrosis Score ≥0.676	3.2%	Not Stated
Grattagliano(159)	Type 2 Diabetes = 24.3% Metabolic Syndrome = 29.7% BMI>=25 = 89.2% BMI>=30 = 46.5%	i) Any Liver Fibrosis (≥F1-F2) ii) Advanced Liver Fibrosis	i) Fibrotest ≥0.32 ii) Fibrotest ≥0.58	i) 53.7% ii) 13.1%	ii) 26.5%
Williamson(160)	Type 2 Diabetes = 100%	i) Any hepatic fibrosis (whole study population) ii) Any hepatic fibrosis (NAFLD risk only)	i) Hyaluronic acid (HA) >100ng/ml and no joint disease ii) a) HA as above b) BAAT score (≥2) c) BARD Score (2) d) NAFLD fibrosis score ≥0.676	i/ 5.7% ii) a) 6.1% ii b) 79.3% ii c) 92.6% ii d) 16.4%	ii) 87.5%
Morling(161)	Type 2 Diabetes = 100%	i) Any Liver Fibrosis (whole study population) ii) Any Liver Fibrosis (NAFLD)	i) and ii) a) APRI≥1.0 b) AST:ALT Ratio≥1.0 c) ELF score ≥ 10.358 d) FIB4 ≥1.30 e) TE (Liver Stiffness) ≥8.7 kPa-	**Whole study:** i) a) 0.8% i) b) 22.4% i) c) 7.0% i) d) 68.3% i) e) 4.8%	Not Stated

				NAFLD subgroup: ii) a)0.4% ii) b) 16.7% ii) c) 4.3% ii) d) 63.8% ii) e) 4.8%	
Das(162)	**Whole population:** BMI>=25 = 7% Abdominal Obesity* =11% Dysglycaemia = 13% **NAFLD subgroup:** BMI ≥25 = 25% Abdominal obesity – 39% Dysglycaemia – 26%	Significant Liver Fibrosis	TE (Liver stiffness) ≥8 kPa	1.4% of whole population; 15.9% of NAFLD patients; 59% of NAFLD patients with raised ALT	N/A (subjects selected due to raised ALT)
Wong(54)	Type 2 Diabetes = 11% Metabolic Syndrome = 47.3%	Advanced Liver Fibrosis	a) TE (liver stiffness) ≥ 9.6kPa b) AST:ALT ≥1.0 c) APRI ≥0.5 d) APRI ≥1.5 e) FIB4 ≥1.30 f) FIB4 ≥ 2.67 g) NAFLD Fibrosis Score ≥0.676 h) BARD ≥2	a) 3.7% b) 12.1% c) 4.5% d) 0% e) 9.8% f) 0.4% g) 0% h) 6.1%	Not Stated
Veysey(156)	NAFLD defined by elevated fatty liver index score	Any Liver Fibrosis	NAFLD Fibrosis Score≥0.676	27.9%	Not Stated

ALT = alanine aminotransferase; AST = aspartame aminotransferase; APRI = AST:platelet count ratio; BAAT = score of age≥50 years (1 point), body mass index≥28 (1 point), ALT≥2 times upper limit of normal, triglycerides≥1.7mmol/L; BARD = weighted score of Body mass index ≥28 (1 point), AST:ALT ratio≥0.8 (2 points), Type 2 Diabetes (1 point); BMI = body mass index; ELF = Enhanced Liver Fibrosis (combination of hyaluronic acid, TIMP metallopeptidase inhibitor 1 and Procollagen III N-Terminal Propeptide);FIB4 = combination of age, ALT, AST and platelet count; NFS = NAFLD Fibrosis Score (combination of age, hyperglycemia, body mass index, platelet count, albumin, and AST:ALT ratio);TE = Transient Elastography

Table 5. Results of 3 studies reporting liver fibrosis prevalence in patients with excessive alcohol use					
Study	**Risk Factor Prevalence**	**Outcome Measure**	**Index Test Threshold**	**Disease Prevalence**	**Normal ALT (%) (Diseased State)**
Baba(148)	Not Stated	Any liver fibrosis	TE (liver stiffness) ≥5.9 kPa	14.3%	55%
Sheron(157)	Hazardous alcohol use (Alcohol Audit score>15) = 24.4%	Probable Liver Fibrosis	Southampton Traffic Light 'Red' ≥0.921	11%	87.1%
Moessner(158)	Hazardous alcohol use = 60%	Significant Liver Fibrosis	TE (liver stiffness) ≥8kPa	17%	Not Stated

Southampton Traffic Light Test = combination of hyaluronic acid, Procollagen III N-Terminal Propeptide and platelet count; TE = Transient Elastography

Table 6. Studies reporting factors associated with hepatic fibrosis on logistic regression analysis					
Study	**Outcome Measure**	**Uni- or Multivariate Analysis**	**Variable**	**Odds Ratio (95% CI)**	**P Value**
Baba(148)	Elevated Liver Stiffness (>5.9kPa)	Univariate	BMI 23-25	2.52 (1.23-5.01)	0.012
			BMI >25	3.26 (1.65-6.34)	0.0008
			Alcohol>20g/day	2.12 (1.23-3.70)	0.0075
			Abnormal LFT	3.88 (2.17-6.94)	<0.0001
			Fatty Liver	5.55 (3.11-9.88)	<0.0001
			APRI	2.11 (1.06-3.23)	0.0001
		Multivariate (BMI and alcohol adjusted)	BMI 23-25	2.21 (1.06-4.46)	0.033
			BMI>25	3.25 (1.62-6.43)	0.001
Roulot(155)	Elevated Liver Stiffness (>8kPa)	Univariate	Age>=57 years	2.0 (1.3-3.2)	0.003
			Female Gender	0.5 (0.3-0.7)	0.002
			Ex-smoker	1.7 (1.0-2.8)	0.05
			BMI>=30	3.6 (2.3-5.7)	<0.0001
			Elevated Waist	2.6 (1.7-4.1)	<0.0001
			Circumference	2.0 (1.2-3.2)	0.004
			Triglycerides>150mg/dl	3.1 (2.0-4.8)	<0.0001
			Diabetes	2.9 (1.7-5.1)	0.0002
			Hypertension	3.4 (2.2-5.4)	<0.0001
			GGT>=45IU/L	6.3 (4.0-10.1)	<0.0001
			ALT>=40IU/L	3.7 (1.2-11.3)	0.03
			Platelets<150 10^9/l		
		Multivariate (factors p<0.20 – above plus alcohol	Age>=57 years	1.8 (1.1-3.0)	0.02
			BMI>=30	2.0 (1.0-3.7)	0.04
			Elevated Waist	1.9 (1.0-3.5)	0.05
			Circumference	1.7 (1.0-2.8)	0.03

		consumption)	Diabetes GGT>=45IU/L ALT>=40IU/L	1.7 (1.0-2.9) 4.2 (2.4-7.2)	0.04 <0.0001
Poynard(154)	Presumed Fibrosis	Multivariate	Age Male Gender Waist Circumference Triglycerides Total Cholesterol Fasting Glucose	1.12 (1.10-1.14) 4.31 (2.62-7.08) 1.03 (1.01-1.04) 1.32 (1.21-1.45) 0.61 (0.52-0.72) 1.15 (1.05-1.26)	<0.0001 <0.0001 0.0002 <0.0001 0.04 0.002
	Confirmed Fibrosis	Multivariate	Age Male Gender Waist Circumference Triglycerides	1.13 (1.09-1.16) 6.36 (2.03-22.1) 1.05 (1.02-1.07) 1.22 (1.07-1.39)	<0.0001 0.002 0.001 0.001
Zelber-Sagi(153)	Significant Fibrosis (F1-F2 and above)	Multivariate (Age and Sex adjusted; stepwise comparison)	Age Male Gender Obesity Insulin	1.08 (1.04-1.1) 6.74 (2.6-17.4) 2.30 (1.09-4.8) 1.03 (1.001-1.051)	<0.001 <0.001 0.004 0.007
You(149)	Significant Fibrosis	Multivariate (Age, BMI, HOMA-IR, visceral fat area on CT, calcified carotid plaques and carotid IMT adjusted)	BMI ALT Carotid IMT Number of calcified carotid plaques	1.487 (1.009-2.193) 1.078 (1.015-1.145) 3.244 (1.140-9.234) 1.787 (1.055-3.026)	0.045 0.014 0.027 0.031

ALT = alanine aminotransferase; APRI = AST:platelet count ratio; BMI = body mass index; GGT = gamma-glutamyl transpeptidase; HOMA-IR = Homeostasis model assessment-insulin resistance; IMT = intima-media thickness

Cirrhosis Prevalence

The prevalence of cirrhosis was reported in 6 studies, including 4 studies of unselected patients, 1 study of patients with NAFLD risk factors and 1 study of patients with hazardous alcohol use (see table 7). In the 4 studies with unselected patients, the cirrhosis prevalence ranged from 0.1%-1.7% of the study population. The study in which the highest estimate was obtained (Malik(151)) does not report the study population liver disease risk factor prevalence, so it is unclear if this was a patient population enriched with advanced liver disease. The other 3 studies have liver disease risk factor prevalence in keeping with an unselected population, and provided cirrhosis prevalence estimates of 0.1%-0.76%.

The studies in which the patient population was investigated for specific liver disease risk factors provided higher estimates of cirrhosis than unselected populations. In the study by Moessner(158), cirrhosis prevalence in a population of alcohol and drug misusers was 4%. In the study by Das(162), cirrhosis prevalence in patients with NAFLD was 2.4%. Furthermore, in the Das study it was possible to calculate an estimate for NAFLD cirrhosis within the entire unselected study population of 0.2%.

Table 7. Results of 6 studies reporting cirrhosis using non-invasive biomarkers in a community setting						
Study	**Risk Factor Prevalence**	**Outcome Measure**	**Index Test Threshold**	**Disease Prevalence (%)**	**Cirrhosis Aetiology**	**Normal ALT (%) (Diseased State)**
Roulot(155)	Metabolic syndrome = 20.3% BMI>=30 – 17.1% BMI 25-29 = 45.8%	Cirrhosis	TE – liver stiffness>13kPa	0.76%	Alcohol (56%), Chronic viral hepatitis (44%)	Not Stated
Poynard(154)	Hazardous alcohol 22.5% BMI>=27 – 32.5%	Cirrhosis	Fibrotest>0.48 and TE (liver stiffness) ≥7.1 kPa and liver biopsy confirmation	0.1%	NAFLD and ALD (44%), NAFLD (33%), ALD and Hepatitis C (22%)	Not Stated
Zelber-Sagi(153)	Diabetes = 6.8% Hypertension = 37.3% Metabolic syndrome = 18.6%	Cirrhosis	Fibrotest≥0.75	0.3%	Not Stated	Not Stated
Moessner(158)	Not Stated	Cirrhosis	TE – liver stiffness≥12kPa	4%	ALD (100%)	Not Stated
Malik(151)	Not Stated	Cirrhosis	TE – liver stiffness≥7kPa and liver biopsy confirmation	1.7%	Not Stated	Not Stated
Das(162)	**Whole population**: BMI>=25 = 7% Abdominal Obesity* =11% Dysglycaemia = 13% **NAFLD subgroup**: BMI ≥25 = 25% Abdominal obesity – 39% Dysglycaemia – 26%	Cirrhosis	NAFLD (ultrasound and CT) and raised ALT	0.2% of whole population; 2.4% of those with NAFLD	NAFLD (100%)	Not Stated

Abdominal obesity defined as waist circumference ≥90cm in men or ≥80cm in women; ALD = alcoholic liver disease; ALT = alanine aminotransferase; BMI = body mass index; CT = computerised tomography; kPa = kilopascals; NAFLD = non-alcoholic fatty liver disease; TE = transient elastography

Liver Biopsy Results

No studies performed liver biopsy in all patients undergoing index test measurement. In only 5 studies were liver biopsies performed in patients with elevated index test results as a confirmative measure (see table 8). This includes 4 studies in which TE was the index test and 1 study where Fibrotest was the index test utilised. In a 6th study by Das et al(162), liver biopsy was offered to all patients undergoing TE (of whom 28/44 accepted), although the diagnostic performance of TE compared to liver biopsy was not reported. Thus, it is not possible to report or metaanalyse the diagnostic performance of any of the index tests studied in the community setting.

Of the 4 studies in which patients with elevated TE results were offered a liver biopsy, acceptance rates ranged from 30% to 87.5%. Of note, in the study by Roulot(155) all 9 patients with a liver stiffness measurement >13Kpa underwent liver biopsy and all were confirmed to have cirrhosis (aetiologies: alcohol (5 patients), Hepatitis C (3) and Hepatitis B (1)). Furthermore, 17/18 (94.4%) of patients with liver stiffness values between 8-13kPa who underwent liver biopsy were confirmed to have F1-F3 stage liver fibrosis. Of these, 8 patients (47.1%) had liver fibrosis due to NAFLD and 6 patients (35.3%) due to ALD. In the study by Moessner(158) however, at a similar liver stiffness threshold of 12 kilopascals, the positive predictive value for cirrhosis was only 45%. It should be noted however that patients in this study were predominantly alcohol misusers, in whom liver stiffness values which predict cirrhosis in secondary care studies has been shown to be higher than for other liver disease aetiologies(164). In the study by

Grattagliano(159), 16/34 patients (47.1%) with a Fibrotest reading ≥0.58 (consistent with advanced liver fibrosis) underwent liver biopsy. Of these, 14 patients had advanced liver fibrosis on liver biopsy, consistent with a positive predictive value for advanced fibrosis of 88%.

ALT Levels

The percentage of patients with hepatic fibrosis or cirrhosis and normal serum ALT levels was reported in 9 studies. These percentages provide an estimate of liver disease cases which would be missed based upon traditional liver investigation algorithms commonly used in the primary care setting. Overall, 2 studies by Wong(54) and Grattagliano(159) used the conservative ALT cutoff of >19U/L for women and >30IU/L for men initially suggested by Prati et al(110). The remaining studies utilised more common cutoffs between 35 and 50U/L.

The percentage of patients with liver fibrosis and normal ALT in which populations screened were unselected or age selected alone was reported in 5 studies (see table 3). The range of ALT normality observed was 40%-74.6%. The lowest estimate was observed in the study by Wong where conservative ALT cutoffs were utilised, whilst in 3 of the remaining 4 studies ALT levels were normal in more than 50% of patients with the diseased state.

ALT normality was reported in 3 studies investigating patients with NAFLD risk factors (see table 4). In the study by Grattagliano(159), 26.5% of patients with advanced liver fibrosis still had normal ALT levels despite very conservative ALT thresholds. In the other study by Williamson(160), 87.5%

of patients with elevated hyaluronic acid (and assumed NAFLD) had normal ALT using a more traditional ALT threshold of 50U/L.

The percentage of patients with liver fibrosis due to excessive alcohol use and normal ALT was reported in 2 studies (see table 5). In the study by Sheron(157), 87.1% of patients with an elevated Southampton Traffic light score had normal ALT values, whilst in the study by Baba et al, 55% of patients with elevated liver stiffness (≥5.9 kPa) had normal ALT values. Importantly, both studies recruited patients from population representative of alcohol consumption in their geographic region, rather than alcohol dependent patients alone as would be seen in studies of outreach centres.

The percentage of cirrhosis diagnoses with normal ALT values was not reported in any studies.

Table 8. Results of 5 studies reporting liver biopsy findings in patients with abnormal index test result				
Study	**Index Test Threshold**	**Biopsy Performed**	**Biopsy Results**	**Disease Aetiology**
Roulot(155)	i) TE (Liver Stiffness) 8-13kPa ii) TE (Liver Stiffness) >13kPa	i) 18/80 (22.5%) ii) 9/9 (100%)	i) 17/18 (94%) F1 or F2 fibrosis ii) 9/9 (100%) Cirrhosis	i) NAFLD (8), ALD (6), HBV (2), HCV (1), PBC (1) ii) ALD (5), HCV (3), HBV (1)
Lemoine(150)	TE (Liver Stiffness)≥7.2 kPa	7/8 (87.5%)	All F0-F1 fibrosis stage (individual staging not stated)	Not Stated
Moessner*(158)	TE (Liver Stiffness)≥12 kPa	20/45 (44.4%)	F1 Fibrosis 4/20 (20%) F2 Fibrosis 3/20 (15%) F3 Fibrosis 4/20 (20%) Cirrhosis 9/20 (45%)	Not Stated
Malik(151)	i) TE (Liver Stiffness) 7-10kPa ii) TE (Liver Stiffness) >10kPa	i) 7/18 (38.9%) ii) 4/4 (100%)	i) No fibrosis 7/7 (100%) ii) F3 Fibrosis 2/4 (50%), Cirrhosis 2/4 (50%)	All patients ALD or NAFLD, but exact percentages not stated
Grattagliano(159)	Fibrotest ≥0.58	16/34 (47.1%)	F2 Fibrosis 2/16 (12.5%) F3 Fibrosis 14/16 (87.5%),	Not Stated

*Biopsy data reported in this study includes both Hepatitis C positive and negative patients. ALD = alcoholic liver disease; kPa = kilopascals; HBV = Hepatitis B Virus; HCV = Hepatitis C; NAFLD = Non-alcoholic fatty liver disease; PBC = primary biliary cirrhosis; TE = Transient Elastography

Discussion:

This systematic review identified 18 studies published in full or abstract form which have used non-invasive biomarkers to stratify chronic liver disease in a community setting. General population estimates for the presence of any liver fibrosis were diverse (0.7%-25.7%), probably due to the heterogeneous approaches used by individual studies as discussed in more detail below. However, narrower estimate ranges were reported for significant liver fibrosis (6.9-12.8%), advanced liver fibrosis (0.9-2%) and cirrhosis (0.1-1.7%) in unselected populations.

The presented data suggest in a couple of ways that the true liver disease prevalence is greater than has been detected by investigation algorithms relying upon abnormal liver function blood tests or specific symptoms to instigate investigations for liver disease. Firstly, in the 9 studies in which data were reported, the majority of liver disease cases had normal ALT levels. Even in 2 studies using very conservative ALT thresholds (previously shown to have poor specificity for liver disease(111)) 26.5% and 40% of liver disease cases still had normal ALT levels. Unfortunately, ALT levels were not reported in diagnosed cases of cirrhosis by any studies, therefore the proportion of cirrhosis cases which would remain undetected by usual care remains unknown. However, the range of cirrhosis prevalence reported (0.1%-1.7%) is greater than previous estimates by Fleming(20) and Jepsen(165) of 0.07% and 0.07-0.13% for all-cause cirrhosis and alcohol-related cirrhosis respectively in Northern European populations. This is due in part to database studies using secondary care diagnostic coding, which is usually assigned after presentation with an episode of decompensated liver

disease. Therefore it is likely that the diagnostic yield of cirrhosis, particularly compensated cirrhosis, will also be increased by adopting liver disease screening in the community.

Unsurprisingly, focussing on specific risk factors for liver disease yielded a higher prevalence of liver fibrosis and cirrhosis. For example, a cirrhosis prevalence of 4% was identified in hazardous alcohol users in the study by Moessner(158) and a NAFLD cirrhosis prevalence of 2.4% was identified by Das(162). These are at risk groups which future studies of screening might target to evaluate the feasibility of, and optimal method for, identifying liver disease in these patients.

A large number of non-invasive biomarkers were utilised by the reported studies although only 3 tests (Transient Elastography, Fibrotest and NAFLD Fibrosis Score) were utilised in 3 or more studies. Furthermore, for only 2 of these tests (TE and Fibrotest) were any cases of liver disease confirmed by liver biopsy; these are therefore the most validated tests used to date in a community setting. Abnormalities of TE or Fibrotest appeared to be accurate in selected studies. For example, in the study by Roulot(155) the positive predictive value (PPV) for any fibrosis with a liver stiffness measurement >8kpa was high (96.3%), Malik et al reported a PPV for advanced fibrosis of 100% with liver stiffness >10kpa, and Moessner et al a PPV of 100% for liver fibrosis above 12kPa, although a lower (45%) PPV for cirrhosis was observed at this liver stiffness cutoff. Studies where lower liver stiffness thresholds were utilised (7 and 7.2 kilopascals) had a far lower percentage of patients in which liver fibrosis was confirmed by biopsy. This gives an indication of the liver stiffness threshold which should be utilised in

a community setting to define liver fibrosis. However, possible ascertainment bias should be considered as not all elevated liver stiffness results underwent liver biopsy; the diagnostic performance of TE may therefore be artificially inflated.

The diverse estimates obtained in studies reporting any fibrosis prevalence in the population, highlights a number of limitations of the reported studies. A large number of index tests and variety of threshold values to define liver disease were utilised, some of which had not been previously validated in secondary care studies. Furthermore, these index tests contain diverse variables, or in some studies variables which were also utilised to originally select the study population. The likely inaccuracy of some of these fibrosis estimates is therefore not particularly unexpected, and it is important that future studies utilise index test and index test thresholds which are most relevant to the chosen screening population. Unsurprisingly, studies which reported more advanced liver disease stages (in which diagnostic thresholds will more accurately separately normal and diseased populations) yielded a narrower range of estimates of disease prevalence.

A further limitation is that no studies evaluated the diagnostic performance of index tests compared to liver biopsy, and only several performed liver biopsy in patients with abnormal index test results. However, most studies utilised index test cutoffs which have been validated in secondary care populations and shown to accurately predict liver biopsy findings. In a secondary care population, many of these investigations have diagnostic cutoffs with high negative predictive value but lower positive predictive value, ensuring that cases of liver disease are not missed. In a

primary care population, due to lower disease prevalence than hospital liver clinic populations, the NPV will improve further at the cost of reducing PPV. Using such tests in a community setting is unlikely to miss a significant proportion of liver disease, but will over diagnose cases, resulting in increased cost and unnecessary anxiety for patients with a false positive test result. It is clearly not possible yet to determine a 'one size fits all' algorithm for all general populations from the data published to date, and further study is required to determine the optimal method to screen for liver disease in a community setting.

As discussed above, a possible criticism of many of the reported studies is the lack of validation with a reference test such as liver biopsy. However, liver biopsy of all at-risk individuals in the general population is of course not realistic due to its cost, specialist provision and small but not absent risk of complications. It should also be considered that liver biopsy is an imperfect gold standard due to significant sampling variability and therefore the 'true' diagnostic performance of the studied index tests cannot be shown in large primary care studies. A compromise to this issue would be reserving liver biopsy for patients with elevated biomarker readings but diagnostic uncertainty as to whether they indeed have clinically significant liver disease. Longitudinal outcomes, such as whether non-invasive biomarkers can predict future cirrhosis development, hepatic decompensation or death, are a more relevant reference standard although of course these outcomes take many years to develop. Only 1 published study in the general population by Kim et al(85) has evaluated the prediction of longitudinal outcomes using fibrosis biomarkers in a general population

setting. In this study, simple serum tests (APRI, FIB4 and the NAFLD fibrosis score) predicted all-cause mortality in a community-based population of people with NAFLD. Further studies highlighting the prognostic information given by community biomarker measurement would increase the confidence in their utilisation.

Few studies reported the percentage of eligible patients who agreed to undergo liver disease screening. In the studies where this was reported, only 2 achieved a greater than 50% screening uptake. One of these studies by Moessner(158) was performed at a drug and alcohol outreach centre and therefore represented a captive audience who were more likely to have agreed to undergo the screening investigation. The other study screened patients in a very geographically and culturally distinct rural village in India, and is highly unlikely to represent screening uptake in UK primary care populations. It was also important to note that there was significant patient dropout in studies which performed multiple diagnostic steps as part of their biomarker investigation algorithms. This patient dropout needs to be evaluated against the context of multi-stage algorithms beneficially screening out individuals who do not need more specialist or expensive second step tests.

A further important limitation of the systematic review results from the design of the identified studies. There were no randomised controlled trials identified, and moreover none of the studies performed liver biopsy in either unselected patients or all of those with abnormal biomarker results. Firstly, this meant it was not possible to metaanalyse the diagnostic performance of any of the utilised non-invasive tests and therefore establish their sensitivity

and specificity for detecting liver disease in a community setting. Secondly, this meant that it was not possible to formally evaluate the quality of studies identified – all studies were essentially diagnostic prevalence studies for which a suitable quality screening tool could not be found. Nonetheless, in view of the study methodology limitations described above, or studies would be of low to medium quality which tempers the strength of the conclusions which can be drawn from them.

There are a number of unanswered questions which future studies evaluating liver disease screening should consider. Importantly, further longitudinal studies assessing the prognostic information given by liver disease stratification in the general population in additional to their cross-sectional diagnostic information. This would be particularly pertinent using those index tests which are most validated in the general population, such as TE and Fibrotest. Furthermore the optimal method of diagnosing liver disease in the general population (whether fibrosis or cirrhosis) needs further exploration. This includes defining the risk factors which identify the greatest yield of significant liver disease, validating the diagnostic thresholds of index tests reported in the previous studies and identifying if any of the cheaper serum tests can adequately screen out patients prior to more expensive and specialist investigations such as TE. Lastly, the screening uptake in the previously reported studies has thus far been mediocre, and measures to optimise screening attendance should be considered. This includes qualitative studies of patients in primary care which can explore in depth the experience of patients undergoing liver disease screening and the barriers to liver screening attendance.

In summary, this systematic review has identified 18 studies in a community setting which have utilised a screening or risk factor based approach for chronic liver disease detection. Using non-invasive tests validated in secondary care, of which Transient Elastography is the most studied, results in identification of undetected chronic liver disease cases within the community setting in a diverse set of populations. The majority of cases would have been missed by current referral pathways based upon abnormal liver function tests. However, an optimal strategy for risk stratification is not yet clear and further research is required to determine the most effective approach.

Chapter 3: A Pilot Study Investigating Stratification of Liver Disease Due to Hazardous Alcohol Use or Type 2 Diabetes in a Primary Care Setting

Introduction

As highlighted in the introductory chapter of this thesis, both the incidence and prevalence of cirrhosis, and subsequent liver disease-related mortality, have increased between recent decades in the United Kingdom. This is predominantly due to two main contributors which have already been outlined in detail. These are: i) an increase in risk factors for chronic liver disease due to population lifestyle behaviours (in particular alcohol consumption, obesity and related metabolic syndrome features) and ii) the reliance on insensitive screening tests in primary care (LFTs), with resultant late diagnosis of patients with decompensated cirrhosis where it is more difficult to treat effectively.

Understandably a paradigm shift has begun, with the new approach of utilising newer non-invasive technologies in the community aiming to detect liver disease at an earlier (asymptomatic) stage. The systematic review reported in chapter 2 discusses 18 studies in which screening of patients in the general population has occurred, either of unselected patients, or those with specific risk factors for developing chronic liver disease, and allows a number of preliminary conclusions to be drawn. Overall, these studies reported a prevalence of both hepatic fibrosis and cirrhosis which was greater than larger epidemiological studies, with a significant number of previously undetected liver disease cases diagnosed. Unsurprisingly, studying specific risk factors for liver disease e.g. hazardous alcohol use, or

NAFLD risk factors, increased the pre-test probability of detecting hepatic fibrosis or cirrhosis. Importantly, in studies where elevation of liver enzymes was not a required inclusion criterion for screening, the majority of detected liver disease cases had normal liver enzymes. The most extensively validated index test in a general population setting was Transient Elastography (performed in 10 studies, with confirmatory liver biopsy occurring in 4 studies) with evidence shown of liver stiffness thresholds with a good positive predictive value for detecting liver fibrosis and cirrhosis.

Despite these findings, there remain a number of aspects to primary care liver disease screening which require further study. Within a UK healthcare setting there is limited data of newer non-invasive investigations in primary care. Overall, the systematic review identified only 3 cohorts (totalling 4 research publications) undergoing study in the UK. These were the Edinburgh Type 2 Diabetes study (161, 163) of patients with type 2 diabetes aged 60-74, the ALDdeS study of patients identified with hazardous alcohol use by alcohol AUDIT screening in 9 general practices in Southern England(157), and the BALLETS study of patients with elevated liver function tests in 8 general practices in Birmingham(56).

However, there are important limitations in these prior studies. Firstly, with regards to the selection criteria for study, as BALLETS only investigated patients with elevated LFTs, the true prevalence of NAFLD and NAFLD with elevated NAFLD fibrosis score in the population could not be elicited. Moreover, the Edinburgh Type 2 Diabetes cohort only investigated more elderly diabetic patients. These data are unlikely to be generalizable to all

general practice patients with type 2 diabetes as those patients with earlier mortality due to ischaemic heart disease are also likely to have the greatest risk of progressive NAFLD. Secondly, a large variety of index tests were utilised in these studies and only one study presented data of the most validated index test (Transient Elastography)(161). In addition, none of the study participants underwent liver biopsy to attempt to validate cases of hepatic fibrosis or cirrhosis, therefore it isn't possible to estimate the possible false positive or negative rate of biomarker testing in these cohorts. Thirdly, in the ALDdeS study more than one screening step was used in their algorithm (alcohol AUDIT testing, followed by invitation for blood testing in those with an elevated alcohol AUDIT score). This resulted in a large dropout through the algorithm, with only 38% of those participants returning an AUDIT questionnaire attending clinic for the Southampton Traffic Light blood test. Clearly, further study of liver disease screening algorithms is required in a UK healthcare setting before more widespread adoption of such strategies can be recommended.

Previous studies of liver disease stratification from both the reported primary and secondary care literature have therefore been used to design an evidence based community investigation pathway for liver disease stratification in primary care. The potential of this diagnostic strategy of targeting high risk groups for chronic liver disease with initial non-invasive screening tests was examined. The aims of this initial pilot study were i) to assess the feasibility of implementing this new diagnostic pathway and liver specialist assessment within a community setting, in particular assessing

technological limitations of transient elastography and patient attendance of this novel pathway and ii) in the studied risk factor groups to provide an estimate of the number of previously undiagnosed liver disease cases detected by this new approach.

Methods

Study Setting

This was a prospective pilot study with patient recruitment from two suburban primary care practices in Rushcliffe, Nottingham (the most affluent borough in Nottingham) with a total patient population of 12,368 individuals. A 12 month feasibility study period for biomarker investigation was planned. The first general practice, St George's Medical Practice (SGMP; 8,968 patients) was selected due to a previous working relationship between one of the General Practitioners and the Nottingham University Hospitals Consultant Hepatologists. The second general practice, West Bridgford Health Centre (WBHC; 3,400 patients) is nearby to SGMP, although it is a completely independent practice. Patients recruited at WBCH were investigated and reviewed at the SGMP site due to greater room availability in the latter general practice site. Both practices utilise the same electronic database (SystmOne; TPP, United Kingdom) for longitudinal collection of clinical, anthropometric and biochemical patient data. During routine GP and practice nurse appointments, data is inputted live into the database and stored as numeric data or prospectively coded with relevant 'Read Codes'. Subsequently, all patients with a specific numeric variable or Read Code can be identified via a search feature within SystmOne.

Patient Selection

From the SystmOne database used in the practices, adult patients (aged 18 years or older) with selected risk factors for lifestyle related chronic liver disease during the study period were identified. SystmOne search strategies were produced in collaboration with the Senior GP Partner (Dr Matthew Jelpke) at SGMP. Patients were eligible for study inclusion if identified with one or more of the chronic liver disease risk factors below. Importantly, due to the poor sensitivity of liver function enzymes for detecting hepatic fibrosis, patients with normal liver function enzymes were considered eligible for inclusion within the study.

a) Hazardous alcohol use:

A previous study using The Health Improvement Network (THIN) revealed that alcohol consumption coding in UK primary care is heterogeneous. In a review of newly registered patients between 2007 and 2009 with alcohol screening data in 500 UK general practice centres(166) (equivalent to 6% of UK primary care patients), 39% had a READ code for levels of consumption (e.g. hazardous or harmful alcohol use), 43% a READ code of numeric alcohol consumption per week (i.e. units consumed per week), and 2% had a screening questionnaire test (e.g. alcohol AUDIT test). The remaining 16% had more than one category coded in their GP records.

Therefore, to optimise the sensitivity for detecting participants with hazardous alcohol use from the GP records, multiple search criteria were used to define hazardous alcohol use. These were i) a numerical search of alcohol consumption (units per week) defined as >14 units per week alcohol consumption for women or >21 units per week alcohol consumption for men;

ii) presence of READ codes related to alcohol misuse (see Appendix C) or iii) alcohol AUDIT questionnaire score of 8 or more. The alcohol AUDIT tool was introduced by the participating practices in 2011 as part of new patient appointments, and has been shown previously to have a 92% sensitivity and 94% specificity for detecting alcohol misuse(167).

b) Type 2 Diabetes:

A preliminary search of SystmOne revealed that the participating practices had 1,320 patients who were obese with a body mass index of ≥30kg/m^2, although overall only 87% of total adult patients had a body mass index value recorded. It was felt unfeasible to screen patients at risk of NAFLD due to obesity during the planned 12 month study period.

In the Verona cohort, people with type 2 diabetes were shown to have a hazard ratio of 2.52 (95% CI 1.96-3.20) for cirrhosis-related death compared to the general population(74). Further studies have shown that in NAFLD, those with type 2 diabetes have an increased risk of advanced liver fibrosis(70), fibrosis progression(82), hepatocellular carcinoma(72) and liver-related death(168, 169). Therefore type 2 diabetes was screened as a risk factor for liver disease, as this represents the group of NAFLD patients at greatest risk of adverse events. Patients with type 2 diabetes were identified using relevant READ codes related to type 2 diabetes (see Appendix C). Patient records were then hand searched in order to exclude patients with type 1 or gestational diabetes. Patients with impaired glucose tolerance or impaired fasting glucose (i.e. pre-diabetes states) were not included in the study unless developing incident type 2 diabetes during the study period.

c) Raised ALT with negative serological tests:

Conventional liver investigation pathways rely upon raised transaminase results to initiate referral to secondary care for investigation of liver disease. At the request of the participating GPs, a specific group of patients with elevated liver enzymes were considered. This was defined as patients with persistently elevated serum alanine aminotransferase (ALT) levels (≥2 consecutive occasions at least 8 weeks apart), normal liver serology testing for autoimmune, viral and genetic causes of liver disease, without type 2 diabetes or hazardous alcohol use and no other relevant reason for transaminase elevation (e.g, congestive cardiac failure, malignancy or medication use). Local laboratory cut-offs denoting elevated ALT were utilised, which are >35U/L for women and >45U/L for men. Importantly, as routine Gamma-glutamyl transpeptidase (GGT) testing was discontinued at Nottingham University Hospitals in mid-2012, patients with elevated GGT alone were not investigated.

A number of criteria were utilised to exclude identified patients from the study a priori:

i) Definitive evidence of hepatic fibrosis or cirrhosis from previous investigation, defined as biopsy proven liver fibrosis or signs of decompensated liver disease. Patients previously investigated in hepatology clinic who did not have definitive liver fibrosis staging and were not under active hospital follow up were still eligible for study.

ii) There was a contraindication to performing Transient Elastography (namely pregnancy or indwelling cardiac device such as a permanent pacemaker or implantable cardioverter defibrillator)

iii) Patients unable to consent to investigation due to moderate to severe cognitive impairment

iv) Patients who were housebound due to co-morbidities and could therefore not attend the GP practice for investigation

v) Patients with metastatic malignancy

Eligible patients were invited to the study via differing mechanisms. Patients with type 2 diabetes undergo at least a yearly appointment with a specialist diabetes nurse as part of their ongoing type 2 diabetes care. They were therefore invited to the study opportunistically at their diabetes annual review. Those patients not undergoing diabetes annual review during the study period were invited to the study via a letter. Patients with hazardous alcohol use were invited opportunistically during GP appointments, or via letter where they did not undergo a consultation during the study period. Patients with raised ALT were referred by the general practitioners for study as part of their investigation for suspected liver disease. In all cases prior to attendance for the TE scan, a member of the research team (DH or nurses performing the TE) explained the reasons for invitation for investigations and the nature of the test via telephone consultation, and an information sheet was sent regarding TE itself.

Diagnostic Pathway

A novel biomarker pathway (Appendix D) was developed to investigate patients within this study; this was devised from information gained from the systematic review of previous general population studies displayed in Chapter 2 of the thesis and the secondary care literature. A two stage biomarker investigation pathway was used; an initial simple blood test (AST:ALT ratio or BARD score), followed by an imaging test (Transient Elastography). This was done to identify the patient dropout from such an approach, which has been subject to limited study previously, but also felt it would be likely that adoption of a new investigation pathway at a regional or national level would require an initial cheap investigation to limit the number of patients requiring a more expensive and specialist second liver test.

Stage 1 - Simple blood biomarker test (AST:ALT ratio and BARD score)

Patients who agreed to participate in the study initially underwent a simple blood biomarker test. The aim was to utilise a cheap and simple test to limit the number of patients requiring further testing, but with a high negative predictive value to accurately rule out hepatic fibrosis. Blood testing was performed at the general practice site, and blood tests subsequently analysed in the hospital laboratory. From the studies reviewed in chapter 2, there were limited data on the use of such tests in a primary care population, and thus data from hospital-based studies were also considered to identify the appropriate tests.

Several secondary care studies have examined the use of simple blood-based biomarkers for the prediction of fibrosis in cohorts of patients with alcohol-related liver disease(164, 170-175). Overall, the performance of

these tests has been mediocre to poor. However in a study of 439 patients admitted to an alcohol dependence unit(175), including 313 patients with alcohol withdrawal, 78 patients with somatic diagnoses and 48 patients admitted with complications of alcoholic cirrhosis, the AST:ALT ratio had good discriminatory value between the 3 studied groups, and only 8% of the cirrhosis group had an AST:ALT ratio less than 1.0. Furthermore, the AST:ALT ratio has been shown to reflect disease severity in a number of other chronic liver diseases, including autoimmune liver disease(176) and hepatitis C(177, 178). The AST:ALT ratio was utilised as the first step biomarker investigation for participants with hazardous alcohol use. Given that the aim was to identify cases of earlier liver fibrosis in addition to cirrhosis, and the lack of previous data of utilisation in a community setting, a lower diagnostic threshold than the Nyblom study of 0.8 was selected to identify those at increased risk of liver disease and requiring further testing.

A far greater number of secondary care studies have examined simple blood-based biomarkers in patients with non-alcoholic fatty liver disease (NAFLD). One such investigation is the BARD score, a derivative of the AST:ALT ratio, which was utilised as the first step investigation in the groups with type 2 diabetes or raised ALT. The BARD score is a weighted score comprising body mass index≥28kg/m^2 (1 point), AST:ALT ratio ≥0.8 (2 points) and type 2 diabetes (1 point). It was derived in a study of 827 biopsy confirmed cases of NAFLD. A BARD score of ≥2 yielded an odds ratio of 17 for the presence of advanced fibrosis compared to lower scores, and had a negative predictive value of 96% for advanced fibrosis. Of note, this was a significant improvement over the odds ratio of AST:ALT≥0.8 alone (OR 9.3;

95% CI 6.3-13.6). The high negative predictive value of BARD score has been confirmed in several independent cohorts of NAFLD patients(179-181), and importantly remains in NAFLD patients with normal ALT levels(182, 183). In keeping with these previous studies, a diagnostic threshold of 2 or greater was utilised to define those patients with type 2 diabetes or raised ALT at increased risk and therefore requiring further testing.

Patients with normal blood biomarker test results were discharged from the investigation pathway at this stage and required no further liver disease investigation.

Stage 2 - Transient Elastography (Fibroscan)

TE is a non-invasive imaging method derived from ultrasonography, which provides a numerical measurement of liver stiffness, and was initially utilised in the dairy industry in the early 2000s. It has subsequently been developed and validated as an accurate marker of liver fibrosis.

The TE technology consists of a transducer probe which is a modification of a traditional ultrasound probe with an additional vibrating axis at its tip. The probe, covered in gel, is placed between the patient's ribs overlying the right lobe of the liver, with the patient lying in the dorsal decubitus position and their right arm held in maximal abduction(184). The operator, with the assistance of ultrasonic time-motion image, locates a portion of liver substance at least 6cm thick and free of large vascular structures and large bile ducts. The operator then presses a button which results in acquisition of a liver stiffness measurement. During this process, the vibrating axis at the tip of the transducer probe generates low frequency

(50Hz) elastic waves which are propagated through the liver substance. The velocity of the elastic waves as they travel through the liver is measured and is directly related to tissue elasticity(185). Using the standard M-probe, a measurement depth of 25-65mm below the skin surface is selected by the machine software. An XL probe, which measures the liver at a depth of 35-75mm, has also been developed. Any acquisitions with an inappropriate vibrational shape or inadequate follow-up of propagation of the elastic wave are automatically rejected by the software. Results of individual acquisitions are displayed as liver stiffness, measured in kilopascals (kPa) which are shown in real time during the scanning procedure. Other results demonstrated by the machine software, used to define the reliability of the procedure are i) Liver stiffness median (the median reading of all successfully acquired liver stiffness measurements), ii) the Interquartile Range (IQR) of liver stiffness measurements and iii) the success rate (defined as the ratio of successful liver stiffness acquisitions over total liver stiffness acquisition attempts). Typically, the whole examination process for liver stiffness acquisition take 3-5 minutes.

Since its development, a large number of studies have validated the good diagnostic accuracy of Transient Elastography compared to liver biopsy as the gold standard for predicting liver fibrosis staging. The most comprehensive meta-analysis examined 50 studies which used it to stratify liver fibrosis stage in secondary care; totalling more than 9,000 patients and every major cause of chronic liver disease(186). This included 12 studies in which patients with ALD were enrolled and 9 studies in which NAFLD patients were included. Overall, the diagnostic accuracy of TE for individual

stages of liver fibrosis (measured by area under the receiver operator curve characteristic (AUROC)) was good to excellent. The AUROC for significant (F2) fibrosis was 0.84 (with optimal diagnostic threshold of 7.65 kilopascals), for advanced (F3) fibrosis was 0.89, and for cirrhosis was 0.94 (with optimal diagnostic threshold of 13.01 kilopascals).

As described in the systematic review in the previous chapter, TE use in primary care has been subject to far fewer studies, however high positive predictive values for any liver fibrosis and cirrhosis were demonstrated in the French population study by Roulot using liver stiffness thresholds of 8 kilopascals and 13 kilopascals respectively(155).

For the current study, patients with a high blood biomarker result were invited to undergo further liver disease stratification with transient elastography (TE), which was performed in the general practice setting. Non-attenders for the initial TE appointment received a second and final invitation for TE, after which further non-attendance resulted in discharge from the investigation pathway.

The M probe of the portable Fibroscan FS402 device (Echosens, Paris) was utilised for liver stiffness acquisition at the general practice. However, patients with a body mass index (BMI) of ≥35kg/m^2 underwent TE at the hospital setting using the XL probe due to the high risk of scan failures using the M probe in these patients. This is because abdominal obesity increases the skin to liver capsule distance, and is the most uniformly reported predictor of failed or unreliable liver stiffness acquisition(187-189). BMI of 35 or greater is the threshold at which a clinically significant increased rate of invalid scans occurs. This was demonstrated by Myers et al, who

investigated 276 patients with BMI>28 who underwent paired M and XL probe based liver stiffness measurement(190). In these more challenging to scan patients, there was a 16% failure rate in M Probe measurements versus only 1% failure with XL probe. The M probe failures rose rapidly with increasing BMI and were 0% if BMI<30, 6.9% if BMI 30-35, 19% if BMI 35-40 and 59% if BMI>40.

TE measurement was performed by one of 3 nurses, who had performed more than 50 examinations in the hospital nurse-led TE service. Prior to study commencement, secondary care utilisation of TE at Queens Medical Centre, Nottingham was reported in a separate research study(191). Between May 2009 and May 2011, 208 patients had undergone TE on the same day as liver biopsy as part of a nurse-led investigation service. The study showed that valid and reliable liver stiffness measures were achieved in 95% of patients, with good sensitivity and specificity achieved using a diagnostic threshold of 8 kilopascals to predict significant fibrosis on liver biopsy. Moreover, it has previously been reported that operator experience is a predictor of scan validity rate(192), whilst inter- and intraobserver agreement with TE is excellent in experienced hands(193). Using experienced nursing staff to perform TE in the community should therefore optimise scan validity and diagnostic accuracy.

Consistent with local practice at the hospital-based TE service, attending patients were advised to have only a light meal on the morning of their scan appointment. It is worth noting that towards the end of the study

period, a study by Arena et al of 125 patients with chronic hepatitis C undergoing TE revealed significantly increased liver stiffness 15-45 minutes following a 600 calorie test meal(194). However, as these data only became known 2 months prior to study completion, and a statistically rather than clinically significant liver stiffness rise was observed in Arena et al study, we did not change advice to patients regarding mealtimes during the study period.

At the time of study design and initiation, metaanalyses of TE use in individual cirrhosis aetiologies (alcohol and NAFLD) had not been published. Therefore information from the previously mentioned primary and secondary care studies was used to derive a diagnostic threshold for elevated liver stiffness for use in all patients undergoing TE in the current study. Subsequently, a liver stiffness cutoff of 8 kilopascals was used to determine elevated liver stiffness and therefore clinically significant liver disease.

A scan failure was defined as the inability to obtain 10 valid elastography measurements on a single patient. A successful TE result was deemed unreliable if liver stiffness was ≥7.1 kilopascals and the interquartile range divided by median (IQR/median) was greater than 0.3(195, 196). This was in accordance with changes to reliability criteria adopted by Echosens during the early study period. The new reliability criteria were derived in a French study of 1,165 individuals and achieved significant reduction in unreliable results (from 24.3% to 9.1%) without a loss in diagnostic performance(195). Patients with a scan failure in the general practice setting were asked to undergo a second attempt at liver stiffness acquisition using

the XL probe in the hospital setting. All patients, regardless of TE threshold result, received brief lifestyle advice from the nurses and were given the British Liver Trust 'Looking After Your Liver' leaflet as part of this lifestyle intervention.

Patients with a liver stiffness reading of less than 8kPa, or those with persistent scan failure, were discharged from the investigation pathway. Patients with elevated liver stiffness results (≥8kPa), including high but unreliable acquisitions, were reviewed by a consultant hepatologist in an appointment at the general practice. In all community clinic appointments the consultant hepatologist led the patient consultation, but DH was present to facilitate use of the primary care electronic database. The need for liver biopsy as a confirmatory test was considered following an individualised discussion of the risks and benefits of doing so based upon their liver stiffness results and previous general practice investigations. Where appropriate, further investigations including ultrasonography, liver biopsy and enrolment into cirrhosis surveillance programmes, were organised after this consultation. Cirrhosis was not defined by TE result alone, but rather in combination with other investigation information including laboratory tests (presence of thrombocytopenia), ultrasonography (nodular liver appearance, or features of portal hypertension) or histological assessment where performed.

Statistics

An analysis was performed to compare the clinical, anthropometric and laboratory test data between patients with normal and elevated liver

stiffness. Obesity was defined as body mass index ≥30kg/m^2, whilst metabolic syndrome was defined according to the International Diabetes Federation classification of obesity plus 2 of raised blood pressure, raised triglycerides, reduced HDL cholesterol or raised fasting plasma glucose(197).

I also sought to establish the number of diagnosed liver disease cases with normal liver enzyme levels, to indicate those cases which would remain undetected by standard care practice of referral for investigation on the basis of raised liver enzymes. As stated previously, GGT analysis was removed from the panel of liver function enzymes reported by Nottingham University Hospitals in 2012. Therefore, alanine aminotransferase (ALT) levels are the locally used liver function enzyme prompting consideration of hepatology clinic referral. Separate analyses were performed using 2 ALT thresholds; firstly local laboratory cutoffs for elevated ALT (>35U/L for women and >45U/L for men), and secondly more conservative cutoffs outlined in a study of 6,835 healthy blood donors and 131 patients with Hepatitis C viremia by Prati et al (110) (>19U/L for women and >30U/L for men).

Statistical analysis for this pilot study was performed using SPSS version 19.0 (IBM). Categorical data are presented as number (percentage). The Shapiro-Wilk test was utilised to determine whether continuous variables were parametric (normally distributed); a p value of >0.05 suggested that variables were normally distributed. Subsequently, continuous data are presented as mean (standard deviation (SD)) for parametric data, and median (interquartile range) for non-parametric data. Continuous variables were compared using the two sample t test for parametric variables, and

Mann-Whitney test for non-parametric variables. Categorical variables were compared using chi-squared test, or Fisher's exact test if any of the groups in the 2x2 table had fewer than 10 participants present.

Ethical Approval

In August 2011, the Leicester Research Ethics Committee (REC) were contacted and forwarded the study protocol to preliminarily discuss ethical approval for the investigation pathway. Subsequently the Leicester REC provided an ethics waiver, stating that investigations on the pathway and use of cross-sectional patient data did not require ethical approval and this fell under the umbrella of service provision. Nonetheless, during the TE appointment, patients were asked to sign the Nottingham Digestive Diseases Biomedical Research Unit (NDDBRU) Database consent form (10/HO405/8; see appendix E) which in addition facilitated approach for future contact for related research studies.

In May 2013, ethical approval was gained for an ongoing longitudinal cohort study in which participants who undergo TE examinations as part of the Nottingham Community study (13/EM/0123) are asked to consent to longitudinal data collection and contact for qualitative interview and future-related studies. Subsequently, participants who had given consent for the NDDBRU database study during this pilot Rushcliffe phase were retrospectively contacted for consent to this longitudinal cohort study.

Results

Study Population

The total patient population of the two participating general practices was 12,368, of whom 10,479 patients were adults. Upon searching the practice SystmOne database, 5,922 adult patients (56.5%) had alcohol consumption documented, with 6.3% of the adult practice population (658 patients) meeting at least one of our criteria for hazardous alcohol use. The prevalence of type 2 diabetes in the adult practice population was 3.7% (390 patients). Both of these risk factors were found in 21 patients and thus 1,027 patients were identified for the study.

Overall there were 107 a priori study exclusions. This included 71 patients with significant cognitive impairment, metastatic malignancy, or who were housebound, 22 participants who died or left the general practices early in the study period prior to invitation to the pathway, 8 patients under hepatology follow-up for proven hepatic fibrosis or cirrhosis, and 6 participants who had TE contraindications due to pregnancy or indwelling cardiac device. Therefore 920 were invited to the study (see Figure 2).

Overall 504 patients (54.8%) underwent the simple blood biomarker test (AST:ALT ratio or BARD score). Blood test uptake differed significantly between patients identified with type 2 diabetes and hazardous alcohol users (91.4% vs 37.6%, $p<0.001$). Normal blood biomarker results were found in 62 patients (12.3%). A significantly greater percentage of patients with hazardous alcohol use had normal blood biomarker results compared with

patients with type 2 diabetes (18.2% vs 6.6%, p<0.001). These patients were discharged from the pathway at this stage.

The baseline characteristics of the 504 patients who underwent investigations compared to all adult patients in the general practices are shown in table 9. In addition to an increased prevalence of study selection risk factors, patients who underwent the blood biomarker were in older age categories than the comparative total adult general practice population, more likely to be male (69.8% vs. 49.0%; p<0.001), obese (31.7% vs. 12.6%, p<0.001), and have ischaemic heart disease (12.9% vs. 4.0%; p<0.001), hypertension (42.7% vs. 14.5%;.p<0.001) or hyperlipidaemia (61.5% vs. 20.2%; p<0.001).

In addition to the 62 patients discharged with normal blood biomarker results, a further 60 patients (11.9% of those undergoing the blood test) were uncontactable or refused to undergo TE, and 17 patients did not attend 2 TE appointments (3.8% of those eligible for TE). Meanwhile, the participating GPs referred an additional 13 patients with raised ALT for further investigation. Therefore, in total 378 patients underwent transient elastography.

Figure 2: Patient Flowchart Through Non-Invasive Biomarker Pathway

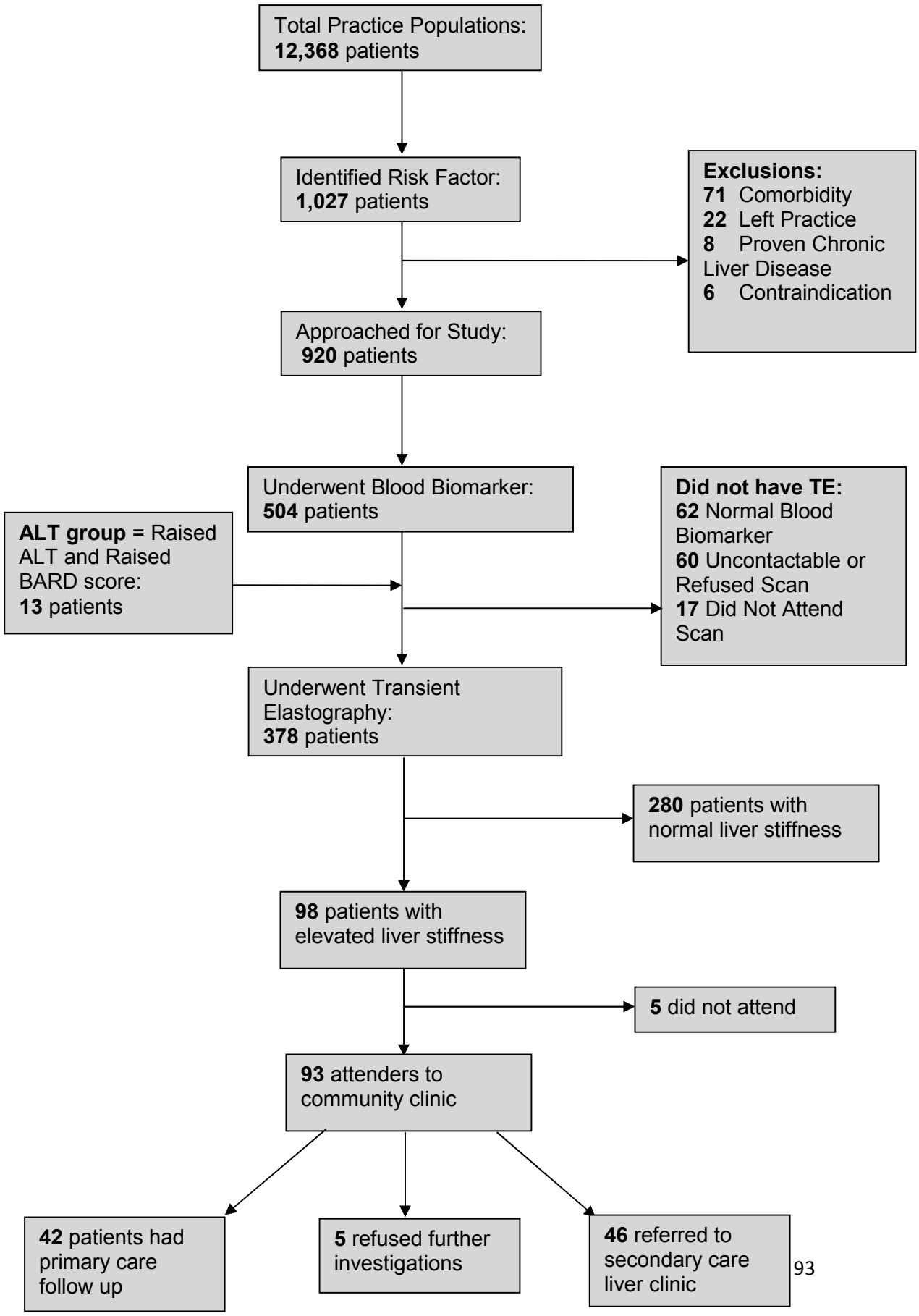


Table 9. Baseline characteristics of all adult patients at studied General Practice sites compared to patients undergoing study			
Variable	**All Adult GP Patients (n=10,479)**	**Patients Undergoing Study* (n=504)**	**P Value**
Age (n%)			
-18-30 years	2100 (20.4%)	20 (4.0%)	**<0.001**
- 31-40 years	2469 (23.6%)	45 (8.9%)	**<0.001**
- 41-50 years	1903 (18.2%)	66 (13.1%)	**0.005**
- 51-60 years	1331 (12.7%)	94 (18.7%)	**<0.001**
- 61-70 years	1287 (12.3%)	131 (26.0%)	**<0.001**
- 71-80 years	781 (7.5%)	103 (20.4%)	**<0.001**
->80 years	608 (5.8%)	45 (8.9%)	**0.005**
Male Gender n(%)	5131 (49.0%)	352 (69.8%)	**<0.001**
Body Mass Index n(%)			
- 25-29.9	2835 (27.1%)	201 (39.9%)	**<0.001**
- ≥30	1320 (12.6%)	160 (31.7%)	**<0.001**
- Missing	1363 (13.0%)	17 (3.4%)	**<0.001**
Hazardous Alcohol Use n(%)	658 (6.3%)	247 (49.0%)	**<0.001**
Type 2 Diabetes n(%)	390 (3.7%)	276 (54.8%)	**<0.001**
Ischaemic Heart Disease n(%)	423 (4.0%)	65 (12.9%)	**<0.001**
Hypertension n(%)	1521 (14.5%)	215 (42.7%)	**<0.001**
Hyperlipidaemia n(%)	2117 (20.2%)	310 (61.5%)	**<0.001**

*Patients undergoing study refers to all patients having the simple blood biomarker step of stratification. Categorical variables are displayed as n(%) and compared using chi-squared test. P values reaching statistical significance ($p \leq 0.05$) are shown in bold.

Figure 3: Distribution of chronic liver disease risk factors for all patients (n=378) undergoing Transient Elastography Examination

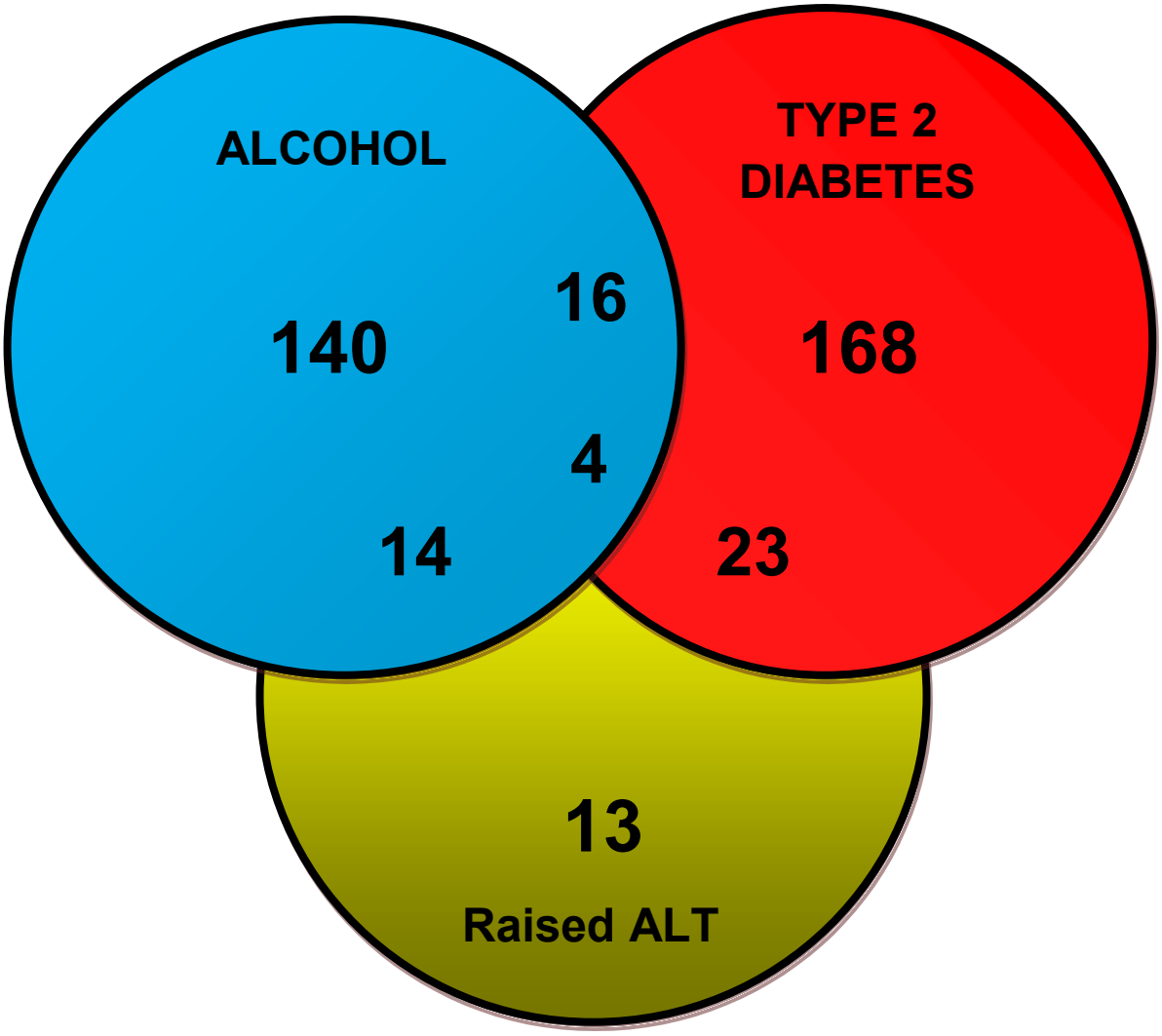


Table 10: Baseline population characteristics of 378 patients with raised blood biomarker result undergoing transient elastography

Variable	All Patients Undergoing TE (n=378)	Hazardous Alcohol Use* (n=174)	Type 2 Diabetes* (n=211)	Raised ALT* (any case) (n=54)
Age – Years	64.0 (53-74)	58.0 (43-65)	70.0 (62-76)	58.0 (49-65)
Male - n(%)	255 (67.5%)	138 (79.3%)	130 (61.6%)	32 (59.3%)
Body Mass Index (kg/m^2)	28.0 (24.95-31.35)	26.3 (24.1-28.4)	29.7 (26.6-32.9)	30.8 (27.3-33.2)
Obesity - n(%)	130 (34.4%)	32 (18.4%)	100 (47.4%)	29 (53.7%)
Hypertension - n(%)	173 (45.8%)	47 (27.0%)	134 (63.5%)	23 (42.6%)
Metabolic Syndrome - n(%)	117 (31.0%)	18 (10.3%)	105 (49.8%)	24 (44.4%)
Ischaemic Heart Disease - n(%)	53 (14.0%)	11 (6.3%)	44 (20.9%)	7 (13.0%)
Type 2 Diabetes - n(%)	211 (55.8%)	20 (5.7%)	211 (100%)	27 (50.0%)
Hazardous Alcohol Use - n(%)	174 (46.0%)	174 (100%)	20 (9.5%)	18 (33.3%)
Current Alcohol Intake (Units/week)	10 (1-28)	28 (22-40)	2 (0-7)	6 (1-25)
Platelets (10^9/L)	237.5 (197-277)	237.5 (198-279)	234 (195-274)	239 (201-272)
Creatinine (µmol/L)	88 (77-99.5)	86 (76-97.5)	88 (77-103)	86.5 (78-93)
Bilirubin (µmol/L)	11 (8-14)	12 (9-14)	11 (8-14)	10 (7-14)
Albumin (g/L)	38 (36-40)	38 (36-40)	38 (36-40)	38 (36-40)
ALT (IU/L)	23 (18-31)	23.5 (18-31)	23 (17-31)	56 (46-68)
AST (IU/L)	24 (20-30)	25 (22-31)	23 (19-28)	42.5 (34-56)
AST:ALT ratio	1.04 (0.84-1.25)	1.11 (0.89-1.35)	0.97 (0.81-1.19)	0.82 (0.75-0.96)

All continuous variables had a Shapiro Wilk normality test p value of ≤0.05, therefore numerical variables are displayed as median (interquartile range (IQR)), categorical variables are displayed as n(%). ALT = alanine aminotransferase, AST = aspartate aminotransferase. **patient numbers refer to patients fulfilling the single risk factor alone or multiple risk factors (see Figure 3).

Chronic Liver Disease Risk Factors Of Those Undergoing TE

The Venn diagram in Figure 3 demonstrates the studied liver disease risk factors of the 378 patients who underwent TE during the pilot study. Overall, hazardous alcohol use was present in 174 patients (46.0%), type 2 diabetes in 211 patients (55.8%), raised ALT in 54 patients (14.3%; includes 13 patients without hazardous alcohol use or type 2 diabetes). Of the patients with raised ALT, only 13 (24.1%) had neither hazardous alcohol use nor type 2 diabetes as a liver disease risk factor. There were 57 patients (15.1% of those undergoing TE) who had more than one chronic liver disease risk factor, including 20 patients with both hazardous alcohol use and type 2 diabetes.

The baseline characteristics for all patients undergoing TE and the individual risk factor groups are shown in Table 10. Both patients with type 2 diabetes and raised ALT were more likely to be obese (BMI≥30kg/m^2; 47.4% and 53.7% respectively) and metabolic syndrome (International Diabetes Federation criteria(197); 49.8% and 44.4% respectively). Laboratory test results were very similar comparing patients with hazardous alcohol use and type 2 diabetes.

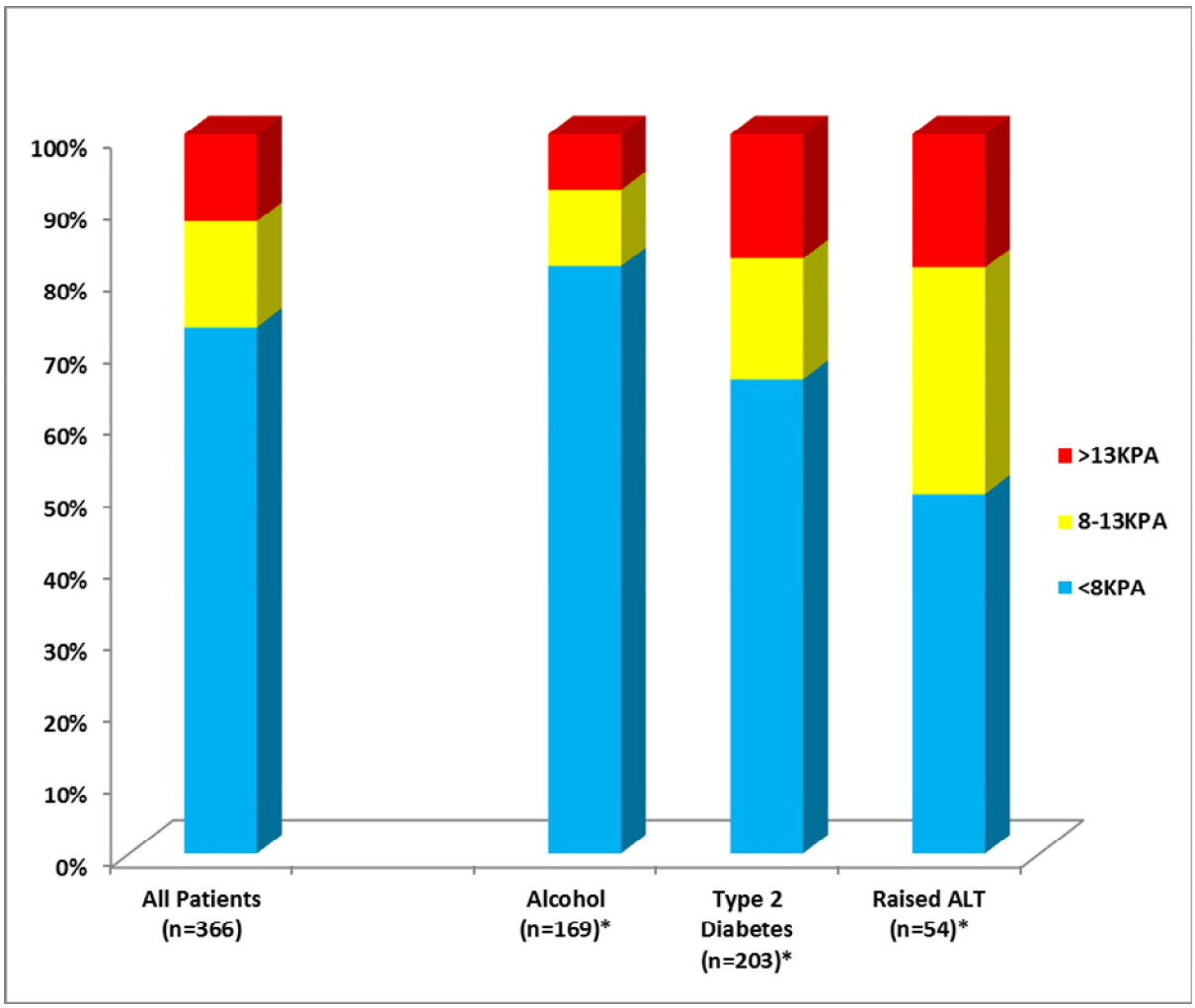
TE Results and Significant Liver Disease Detection

Overall 378 patients attended for a TE appointment; 337 patients (89.2%) had their baseline TE performed at the general practice site using the M Probe and the remaining 41 patients had the TE using the XL probe at the hospital setting. Initial scan failure was seen in 29 patients at the general practice site (8.6%), compared to no patients having their first TE appointment at the hospital. Of these 29 scan failures, 17 went on to have

successful TE measurement using the XL probe at the hospital - therefore it was not possible to obtain a valid liver stiffness measurement in 12 patients (3.2% of all patients undergoing TE). A further 24 patients (6.3%) had an unreliable measurement according to the Boursier criteria (195); 3 of the patients had readings between 7.1kPa and 7.9kPa and were therefore not reviewed by a hepatologist.

Valid liver stiffness acquisition was possible in 366 patients (96.8%). Mean liver stiffness was 7.98 kPa (95% CI 7.22-8.74). Overall 98 patients (26.8% with valid TE) had a liver stiffness measurement ≥8kPa consistent with a new diagnosis of clinically significant liver disease. A significantly greater percentage of patients with type 2 diabetes had elevated liver stiffness compared to hazardous alcohol users (34.0% vs 18.3%, p=<0.001) (Figure 4). Elevated liver stiffness was seen in 50% of patients with raised ALT levels, but in only 4/13 (30.8%) of those without hazardous alcohol use or type 2 diabetes. Patients with more than one defined risk factor (n=56 with successful TE measurement) had a significantly greater percentage of elevated liver stiffness compared with patients with type 2 diabetes alone (49.1% vs 29.5%, p=0.01) or with hazardous alcohol use alone (49.1% vs 14.1%, p<0.001). Liver stiffness readings ≥13kPa were observed in 44 patients (12.0% of those with valid scans) and were seen in 13/169 (7.7%) of patients with hazardous alcohol use, 35/203 (17.2%) of patients with type 2 diabetes, 10/54 (18.5%) with raised ALT and 13/56 (23.2%) with multiple study risk factors.

Figure 4: Transient Elastography results of patients with successful liver stiffness acquisition (n=366)¥



*patient numbers refer to patients fulfilling at least one of these risk factors.

¥excludes 12 patients without valid TE measurement; Hazardous alcohol use (4 patients), type 2 diabetes (7), dual aetiology (1)

A number of clinical features and laboratory test results differed when comparing patients with normal and elevated liver stiffness (see Table 11). Patients with elevated liver stiffness (n=98) were older (median age 66 vs 62 years, p=0.02), had a higher median BMI (30.4 vs 27.2, p<0.001) and higher prevalence of the metabolic syndrome (49% vs 23.5%, p<0.001) than those with normal liver stiffness (n=268). On laboratory testing, patients with elevated liver stiffness had lower platelet count (222.5 vs 241.5, p=0.007), greater prevalence of thrombocytopenia (10.2% vs. 2.6%, p=0.002), higher serum ALT (29.5 vs 22.0, p<0.001), higher serum AST (27.5 vs. 23.0; p<0.001) but lower AST:ALT ratio levels (0.96 vs 1.07, p=0.004) than patients with normal liver stiffness.

Histology Results and Cirrhosis Diagnoses

Of 98 patients referred for community assessment by the consultant hepatologists, 93 (94.9%) attended. Following blood liver screen testing, one unexpected abnormality was detected; a patient with a positive anti mitochondrial antibody M2 subtype (in keeping with likely primary biliary cirrhosis). Overall 42 patients were followed up in primary care by general practitioners, 5 patients refused further follow up, and 46 patients (49.4% of clinic attenders) had a follow up appointment in secondary care (see Figure 2).

Liver biopsy was performed in 25 patients for whom there was diagnostic uncertainty on review of clinical data and TE results (see Figure 5). Median liver biopsy length was 13mm (IQR 7.5-18.0), and 12/25 patients had liver cores ≥15mm. All 25 patients undergoing liver biopsy had an

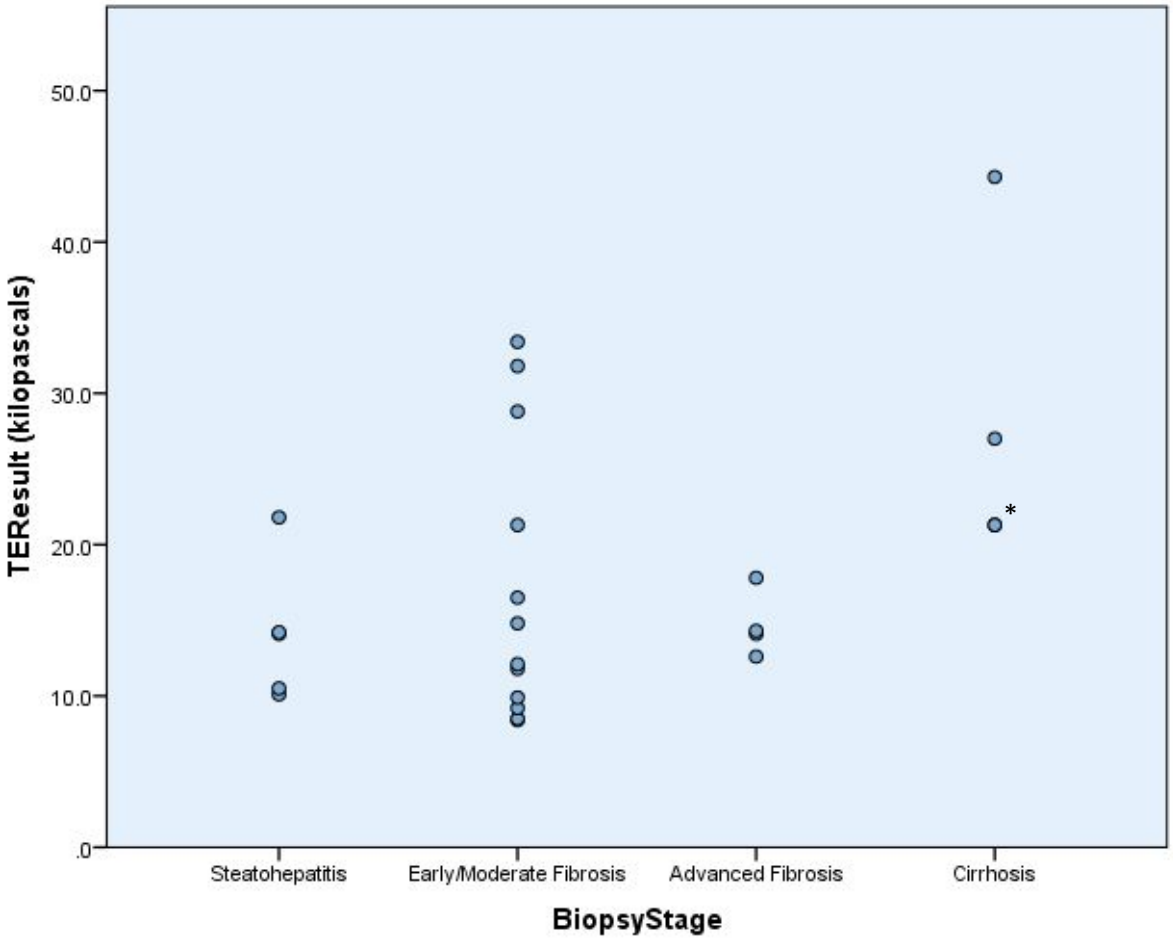
abnormality detected; 5 patients had evidence of steatohepatitis whilst any degree of hepatic fibrosis was confirmed in 20 patients. The liver disease risk factors of patients without hepatic fibrosis on liver biopsy were type 2 diabetes alone in 2 patients, hazardous alcohol use alone in 1 patient , type 2 diabetes and raised ALT in 1 patient and hazardous alcohol use and type 2 diabetes in the final patient. Liver stiffness readings ranged from 10.1 to 21.8 kilopascals in these patients, and none of these scans would have been considered unreliable on quality control criteria. The lowest liver stiffness reading in which a histological diagnosis of advanced fibrosis was made was 12.6kPa, whilst the lowest liver stiffness reading in which a histological diagnosis of cirrhosis was made was 21.3kPa (2 patients).

Overall, 11 patients were newly diagnosed with cirrhosis during the study period, of whom a histological diagnosis was made in 4 patients whilst the others had other diagnostic laboratory tests, radiological tests or endoscopic evidence of cirrhosis. Of the new cirrhosis diagnoses, 4 of these patients had additional hard evidence of portal hypertension (presence of varices at endoscopy, or elevated hepatic venous pressure gradient (HVPG)). Prior to commencing the study, only 8 patients (excluded from recruitment) were known to have cirrhosis in this practice population. Therefore in the absence of a case finding approach such as piloted here, the majority of patients with very advanced liver disease would not have been detected.

Table 11: Comparison of Laboratory Tests and Clinical Features Between Patients with Normal and Elevated Liver Stiffness			
Variable	**Normal Liver Stiffness (n=268)**	**Elevated Liver Stiffness (n=98)**	**P Value**
Age (Years)	62 (49-73)	66 (58-73)	**0.02**
Male - n(%)	175 (65.3%)	71 (72.4%)	0.197
Body Mass Index (g/m^2)	27.2 (24.2-30.4)	30.4 (27.3-33.5)	**<0.001**
Type 2 Diabetes - n(%)	135 (50.4%)	69 (70.4%)	**0.001**
Hazardous Alcohol - n(%)	137 (51.1%)	31 (31.6%)	**0.001**
Raised ALT - n(%)	26 (9.7%)	27(27.6%)	**<0.001**
Multiple Risk Factors n(%)	28 (10.4%)	27 (27.6%)	**<0.001**
Metabolic Syndrome n(%)	63 (23.5%)	48 (49.0%)	**<0.001**
Ischaemic Heart Disease n(%)	31 (11.6%)	19 (19.4%)	0.054
Platelet Count (10^9/L)	241.5 (205.5-279)	222.5 (181-266)	**0.007**
Thrombocytopenia (Platelets<$150x10^9$/L)	7 (2.6%)	10 (10.2%)	**0.002**
ALT (U/L)	22 (17-29)	29.5 (21-45)	**<0.001**
AST (U/L)	23 (19-28.5)	27.5 (22-36)	**<0.001**
Bilirubin (µmol/L)	11 (8-14)	11 (9-16)	0.38
Albumin (g/L)	38 (36-40)	38 (36-40)	0.83
AST:ALT Ratio	1.07 (0.86-1.31)	0.96 (0.79-1.18)	**0.004**

All continuous variables had a Shapiro Wilk normality test p value of ≤0.05, therefore numerical variables are displayed as median (interquartile range (IQR)) and compared using the Mann Whitney test. Categorical variables are displayed as n(%) and compared using chi-squared test. P values reaching statistical significance (p≤0.05) are shown in bold.

Figure 5: Histopathology findings of patients with elevated liver stiffness undergoing liver biopsy (n=25)



*2 patients diagnosed with cirrhosis had TE readings of 21.3 kilopascals

ALT Levels and Liver Disease Diagnoses:

Using the local hospital cut-offs for serum ALT level (>35U/L for women and >45U/L for men) the majority of patients diagnosed with liver disease had a normal ALT level (see table 12). This included 72.4% of patients with elevated liver stiffness readings, 60% of those with biopsy proven liver fibrosis and 90.9% diagnosed with cirrhosis. On the contrary, 49.1% of patients with raised ALT had normal liver stiffness readings consistent with the absence of clinically significant liver disease.

Using the more conservative ALT cutoffs (>19U/L for women and >30U/L for men), 41.8% of patients with elevated liver stiffness readings, 25% with biopsy proven fibrosis and 18.2% with cirrhosis had normal ALT readings. However, using these more conservative ALT values only 39.3% of patients with raised ALT levels had evidence of liver disease on TE, whilst 88 patients (32.8%) with normal liver stiffness would be classified as having raised ALT levels.

Table 12: Serum alanine aminotransferase (ALT) levels of 366 patients with successful liver stiffness acquisition				
Liver Stratification	**Raised ALT Local Lab***	**Normal ALT Local Lab***	**Raised ALT 19/30‡**	**Normal ALT 19/30‡**
Normal Liver Stiffness (n=268)	26 (9.7%)	242 (90.3%)	88 (32.8%)	180 (67.2%)
Elevated Liver Stiffness (n=98)	27 (27.6%)	71 (72.4%)	57 (58.2%)	41 (41.8%)
Cirrhosis (n=11)	1 (9.1%)	10 (90.9%)	9 (81.8%)	2 (18.2%)
Serum ALT levels of 25 patients with elevated liver stiffness undergoing subsequent percutaneous liver biopsy				
No Hepatic Fibrosis (n=5)	1 (20%)	4 (80%)	3 (60%)	2 (40%)
Any Hepatic Fibrosis (n=20)	8 (40%)	12 (60%)	15 (75%)	5 (25%)

Numerical values are displayed as n(%).*Locally utilised cutoffs: ALT>35IU/L for women and >45IU/L for men. ‡Alternative cutoffs: ALT>19IU/L for women and >30IU/L for men. Values are displayed as n(%) in all cases.

Discussion

Statement of Principal Findings

This pilot study uses a novel approach to target patients with risk factors for chronic liver disease with diagnostic tests and consultation with specialists in a community setting. The utilisation of a simple pathway using non-invasive liver fibrosis biomarkers resulted in the detection of a large number of previously undiscovered subclinical, but significant, chronic liver disease cases. This included 98 patients with elevated liver stiffness (26.8% of those with successful liver stiffness measurements), and 11 new cases of cirrhosis in a primary care population of 10,479 adult patients from which our high risk patients were drawn. Given only 8 patients with cirrhosis were known prior to study commencement, the newly identified cirrhosis cases more than doubles the known cirrhosis prevalence in this primary care population. Furthermore, liver disease diagnosis varied significantly according to the identified risk factor; 18% of participants with hazardous alcohol use had elevated liver stiffness, compared to 34% with type 2 diabetes and 49% with multiple liver disease risk factors.

The study also highlights the inadequacy of liver function enzymes as a stratification tool for liver disease in primary care. The majority of new cases of liver disease identified in the study had a normal ALT level. Using the local hospital laboratory cutoffs for ALT, 72% of patients with elevated liver stiffness, 60% with liver fibrosis on biopsy and 91% diagnosed with cirrhosis had normal liver enzymes. Given that an asymptomatic population was studied, their liver disease would have been missed by the standard diagnostic algorithms. Even using much more conservative ALT cutoffs, a

significant number of liver disease diagnoses would be missed, whilst nearly a third of patients with normal liver stiffness would be classified as having an abnormal ALT and subsequently referred for further unnecessary investigations.

The study demonstrates that a diagnostic approach using TE to stratify liver disease is feasible to implement within a UK primary care setting. This pilot study reports the largest number of liver biopsies for abnormal liver stiffness results in primary care, and TE appeared to be an accurate stratification tool. Of 25 patients with elevated liver stiffness agreeing to undergo liver biopsy, all had some histological evidence of liver disease whilst 20 (80%) had histological evidence of liver fibrosis. Non-attendance rates for TE appointments were less than 5%, and nearly 90% of TE scans could be performed in the community setting. Moreover, the nurse-led TE service, which was originally established in secondary care (191), has now been implemented in the community with equivalent quality assurance as evidenced by successful TE acquisition in 96.8% and reliable measurements in 90.5% of cases.

Strengths and Weaknesses of the Study

This study is the first to utilise blood biomarkers followed by Transient Elastography to stratify patients at risk of liver disease in a community population of the United Kingdom. A novel diagnostic pathway was utilised which is rapidly applicable in clinical practice in a large community population of more than 10,000 adults. Targeting patients with well-defined risk factors for liver disease resulted in a high pre-test probability of detecting hepatic

fibrosis, with 26.8% of patients with TE results exceeding the threshold for clinically significant liver disease. This is a far greater diagnostic yield than traditional algorithms using elevated liver enzymes alone to stratify fibrosis risk (56, 95), and is likely therefore to be a cost efficient approach. The use of simple and inexpensive tests as the initial diagnostic, followed by more specialist tests rationalised resource use and enhanced the feasibility of stratifying the large community population. Moreover, evidence based but conservative thresholds were used for the diagnostic tests, to ensure a high negative predictive value (≥93%)(181, 186). Thus, I believe it is unlikely that significant liver disease has been missed within the risk groups that have been stratified. However long term follow up of these patients will be necessary to confirm this.

Clearly, the type of risk factor and presence of multiple risk factors alter the diagnostic yield of the investigation pathway. Therefore, a further strength of the pathway is that it may potentially be applied to regions with a diverse prevalence of liver disease risk factors, with either the tests or thresholds adjusted depending on the initial risk factor(s), and this improves the potential generalizability of our pathway to other healthcare regions.

However, there are several limitations to discuss from the approach used in this pilot study. Patients from specific medical practices within a distinct socio-demographic area of Nottinghamshire (Rushcliffe, the most affluent borough of Nottingham) were investigated. In keeping with this, the detected prevalence of type 2 diabetes, obesity and hazardous alcohol use were lower than national averages. It is possible that both patient attendance

and the detection of clinically significant liver disease may differ elsewhere, and further study of the investigation pathway in other regions is necessary.

The pragmatic study design, both in terms of biomarker selection and investigation of selected risk factors for liver disease, means the sensitivity of the pathway, or the total fibrosis and cirrhosis prevalence in this community population cannot be formally assessed. Alcohol use was only screened in 57% of this community population, which is lower than the approximately 70% documentation of alcohol intake in general medical practices in the East Midlands region(166). I also cannot account for those patients who have underreported their alcohol intake to be within normal limits, which previous questionnaire studies have estimated to occur in 34% of respondents(198). Furthermore, additional risk factors such as obesity and metabolic syndrome, whilst incorporated partially in this pathway (e.g. BARD score) have not been specifically included in this study. Overall, the detected prevalence of significant disease, including cirrhosis represents an underestimate and the presence of cirrhosis in the community is likely to be higher than reported here.

Although data from the 25 patients undergoing liver biopsy suggest that elevated liver stiffness predicts the presence of liver fibrosis in primary care, as shown in Figure 5 the overlap in liver stiffness readings between fibrosis categories was rather large. The reason for this isn't entirely clear, although may be attributable to fewer than half of participants having adequate liver biopsy specimen lengths, and therefore liver biopsy understaging the true degree of liver fibrosis. However, in a primary care

setting where large numbers of patients might need investigation, such strict categorisation of fibrosis stage might be unnecessary. In this population, the value of TE may be limited to discriminating patients with any evidence of liver fibrosis who need intensive lifestyle intervention alone from those with cirrhosis who need additional surveillance measures.

Also of note, patient uptake of screening was not optimal (55% of targeted patients were investigated with the pathway). Patients with type 2 diabetes undergo an annual health check which made them more accessible for opportunistic invitation for screening, and this is one explanation for this significant difference in uptake compared to patients with hazardous alcohol use (91% vs 38% undergoing investigation respectively).

Lastly, there is scope to improve the investigation pathway further. In total only 12% of all patients, and 6% of participants with type 2 diabetes, had normal blood biomarker results and therefore were not required to undergo Transient Elastography. A similar number of participants did not wish to undergo TE despite an abnormal blood test. This suggests that the fewest number of investigation steps as possible should be performed to reduce participant dropout. Future studies should perform TE as a lone investigation, but additionally retrospectively assess whether the use of alternative simple serum fibrosis tests would enable accurate resource utilisation and develop an optimal significant liver disease detection pathway.

What is known and what the study has added to this

Previous studies of chronic liver disease stratification in the general population support our findings of an appreciable burden of previously

undetected chronic liver disease. A study of presumed well army personnel and families in the USA(199), screened 328 participants with ultrasound and liver biopsy for NAFLD. This approach identified a high prevalence of both NASH (12.2%) and significant fibrosis (2.7%). An alternative, non-invasive approach, using transient elastography was employed to screen a defined general population for significant liver disease in France(155). TE was performed in 1,358 asymptomatic patients over the age of 45 from a well person clinic. An elevated reading, above a validated threshold of 8 kilopascals (155) was found in 7% of the cohort and 9 cases of cirrhosis were detected. Importantly both studies used an unselected approach to detect liver disease in the community.

I deliberately focussed the diagnostic tests on individuals with risk factors for liver disease. The pre-test probability of detecting disease is increased using this approach and this is evidenced by the fact that 26% of our cohort undergoing TE had elevated liver stiffness readings compared to 7% in the French study. A risk factor in combination with the elevated biomarker tests also rationalises the use of liver biopsy with a high yield of clinically significant liver disease. In our study the positive predictive value of selected patients undergoing liver biopsy was 80% for detecting any fibrosis. This compares with the 18% positive predictive value of finding any fibrosis on biopsy following investigation of raised liver enzymes in seronegative individuals referred to secondary care(200).

A recent study performed in the UK investigated 1,118 patients with elevated liver enzymes. In those with suspected NAFLD, 7.6 % were found

to have significant disease based upon an elevated NAFLD fibrosis score(56). An important finding from our study is that normal ALT levels, within the local laboratory range, were found in 72% of patients with elevated liver stiffness and 91% of patients with cirrhosis. Thus the reliance on abnormal liver enzymes to detect chronic liver disease, which represents standard clinical practice, is inherently flawed. In NAFLD, the presence of significant liver disease in the context of normal enzymes is well documented. The entire spectrum of NAFLD severity has been shown to exist in patients with normal liver enzymes; multiple studies have observed no difference in disease severity between this group and those with abnormal liver enzymes(102, 104, 106).

Interestingly, if more conservative thresholds are utilised in our population at the 19/30U/L cutoff as advocated by the work of Prati et al (110) then a normal ALT is still observed in 42% of individuals with elevated liver stiffness and 18% with cirrhosis. In those patients with an elevated ALT, 13 patients (24%) did not have type 2 diabetes or hazardous alcohol use as a co-morbidity. Only 4 out of these 13 patients had an abnormal TE reading. Thus, our work strongly supports the concept that the risk for chronic liver disease is better encapsulated by the underlying risk factor as opposed to liver enzyme tests alone.

The ALDdeS study, which investigated participants from 8 primary care practices in Southern England with hazardous alcohol use, used a similar two step approach for patient investigation(157). In their study, patients firstly returned an Alcohol AUDIT questionnaire, and those identified

with hazardous alcohol use were invited to a clinic appointment to undergo a subsequent blood test. The dropout between investigation steps was large, with only 38% of those who were invited attending the clinic appointment. Although this dropout was not as significant in the current study, still 60 patients with abnormal blood biomarker results did not wish to undergo TE. Unless an additional screening step significantly reduces resource use (in this case, the number of people who require TE), it should clearly be avoided to prevent participant dropout. In the current study, several clinical and laboratory test abnormalities were more prevalent in patients with elevated liver stiffness (including obesity, metabolic syndrome and thrombocytopenia) and therefore might accurately exclude the need for a large number of patients to undergo TE. However, this needs further study in a cohort undergoing TE as a single investigation step to establish the diagnostic accuracy of such differing approaches.

Implications

The utilisation of a simple investigation pathway in the community resulted in the detection of a large number of cases of previously unidentified chronic liver disease. Whilst the detection of these new cases is currently of unproven benefit, there are likely to be a number of advantages.

Firstly, early identification of asymptomatic liver disease is likely to reduce future liver-related morbidity and mortality. Interventions for lifestyle-related disease risk factors form established treatments (such as Brief Interventions for alcohol, or dietary and exercise advice), can be performed in a community setting(94, 201) and are cost effective (202, 203). A decision

analysis study which modelled early identification of NAFLD and subsequent lifestyle or medical intervention showed a 41% relative risk reduction in liver-related mortality at 5 years, compared with a strategy of not investigating these patients(204). Furthermore detection of compensated cirrhosis whilst patients are asymptomatic and ambulatory, with enrolment into surveillance programmes for varices and hepatocellular carcinoma detection, reduces mortality and morbidity (13, 205, 206), and also reduces the expensive healthcare utilisation of the decompensated state.

Secondly, early identification of chronic liver disease is likely to be cost effective compared to traditional investigation algorithms. The investigation of liver disease in specialist centres can be both expensive for the healthcare system and inconvenient to the patient. Recent economic modelling from York has suggested that the substitution of elastography for liver biopsy in a secondary care setting would save £520 per patient investigated(131). Implementing these services in the community is likely to improve the health economic benefits of early liver disease detection yet further, although future health-economic modelling studies are required to confirm this.

Lastly, there are no current medical treatments with widely proven efficacy to prevent fibrosis progression in either alcohol-related liver disease or NAFLD. Novel investigation pathways, such as the one presented, identify a population of patients with clinically significant liver disease in whom appropriate therapies may be tested and developed. These, in conjunction with wider adoption of health-related lifestyle changes, may enable reduction

of disease progression, symptomatic liver disease, and liver disease related deaths at a general population level.

Conclusions

A novel diagnostic approach utilised in the general population by identifying patients with chronic liver disease risk factors and stratifying using non-invasive fibrosis biomarkers. This pathway was feasible to implement and resulted in increased detection of asymptomatic but clinically significant liver disease compared to traditional liver-enzyme based algorithms, including more than doubling the identified cirrhosis prevalence. The majority of patients diagnosed with significant liver disease had normal liver function enzymes and would be missed by traditional investigation algorithms. Further study is warranted to ensure the generalizability of our findings to community populations with differing socioeconomic status and prevalence of liver disease risk factors. This would allow a more realistic estimate of liver fibrosis and cirrhosis prevalence in primary care if more accurate screening methods such as TE are utilised. Furthermore, the utilisation of TE as a single investigative tool in primary care investigation pathways would allow identification of the optimal biomarker investigation steps required for detecting clinically significant liver disease.

Chapter 4: Investigating liver cirrhosis diagnoses, the impact of obesity on elevated liver stiffness and cirrhosis and simple fibrosis markers in a primary care setting using Transient Elastography

Introduction:

Chapter 3 demonstrated pilot experience of investigating patients with defined risk factors for chronic liver disease in 2 general practices in Rushcliffe, Nottingham using non-invasive biomarker tests including Transient Elastography. The pilot study showed that in an adult general practice population of more than 10,000 patients, a liver investigation pathway using TE was feasible to implement. Overall valid TE measurements could be obtained in 97% of patients and a significant number of new cases of elevated liver stiffness, fibrosis and cirrhosis could be identified using this approach.

Nonetheless, there were limitations to the approach which was used which limit the generalizability of the pilot study findings to other primary care settings. The first major limitation was that the 2 general practice sites were located in the most affluent borough of Nottingham (Rushcliffe). Associated with this, the prevalence of obesity (12.6%; although 13% of practice adults did not have body mass index values recorded), type 2 diabetes (3.7%) and hazardous alcohol consumption (6.3%) were lower than the respective UK prevalences. Therefore, it is not accurate to compare the prevalence of detected cirrhosis in particular to previous UK population estimates, and elevated liver stiffness prevalence may differ markedly in alternative general practice regions. A subsequent study in a different general practice

population is likely to generate data and conclusions which are more robust and generalizable to UK primary care practice.

In England, cirrhosis incidence has increased by 50.6% between 1998 and 2009(21), and subsequently cirrhosis is now the third commonest cause of premature mortality in persons aged 20-54(19). Due to a continued increase in lifestyle-related risk factors, chronic liver disease will continue to be a significant public health issue for many years to come. Population level alcohol consumption is still considered the major driver of liver-related mortality(16), and up to 62% of detected cirrhosis cases in the population are attributed to alcoholic liver disease (ALD)(14, 21). 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 UK has risen by 54% in men and 65% in women between 1993 and 2012(207), and the prevalence of type 2 diabetes is forecast to double between 2000 and 2030(208). NAFLD is therefore likely to become the leading cause of cirrhosis in the near future, and indeed in the USA NAFLD has already overtaken ALD as a cause of listing for liver transplantation(58).

Obesity has been demonstrated as a risk factor for progressive fibrosis in all major causes of liver disease(209). In particular, several studies have demonstrated the important synergism between body mass index and alcohol consumption, and the increased risk of steatosis (52), progressive fibrosis(210), cirrhosis diagnoses(211) and liver-related death(33, 34). 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 diagnoses in those with an alcohol consumption above the cut-off will be coded as alcohol related cirrhosis(48). 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. However, the true prevalence of clinically significant liver disease in these populations is not known, nor the relative contributions of hazardous alcohol and metabolic risk factor both alone and in combination. Eliciting this would allow development of well-informed and relevant public health policy for lifestyle-related risk factors to avert the trend of rising liver disease mortality.

A second major limitation is that the pilot study used a two-step biomarker algorithm, the first of which was a simple blood-based biomarker (AST:ALT ratio for hazardous alcohol users and BARD score for patients with type 2 diabetes or raised ALT). These investigations only screened out a small number of patients who did not require TE (12% of the overall study population, and only 6% of participants with type 2 diabetes), whilst a similar number of dropouts occurred at this stage from subsequent refusal or non-attendance for TE. Therefore, to justify such a two-step approach, the simple blood test would need both a high negative predictive value to accurately rule out significant liver disease, but would also need to screen out a relatively large number of participants who did not require the more specialist second investigation. In order to analyse the diagnostic accuracy of alternative

approaches requires a change to the current study pathway by using a single investigation (TE) as the gold standard measure of liver disease.

There are a number of simple liver fibrosis tests which can be calculated from laboratory indices which are routinely collected in general practice. A summary of the AST:ALT ratio and BARD score has been provided in Chapter 3. In addition, three other simple fibrosis tests are commonly studied in hospital-based NAFLD populations. These are APRI (AST:platelet index), FIB4 (a panel of AST, ALT, age and platelet count) and the NAFLD fibrosis score (a panel of age, body mass index, type 2 diabetes, AST:ALT, platelet count and albumin). APRI and FIB4 were initially derived as predictors of hepatic fibrosis in patient populations with chronic hepatitis C, and subsequently validated in NAFLD populations. The NAFLD fibrosis score (NFS) was derived in a large hospital-based cohort of 733 NAFLD patients in the US(212). It provides a result in one of three risk categories; patients with NFS below a low risk threshold (-1.455) had a negative predictive value of 93% to rule out advanced liver fibrosis, whilst patients with an NFS score above a high risk threshold (0.676) had a positive predictive value of 90% for advanced liver fibrosis on liver biopsy.

All of the above simple fibrosis tests have been evaluated in several secondary care studies of patients with NAFLD, with excellent negative predictive values for advanced liver fibrosis of 90-98% when compared to liver biopsy(179-183, 213-218), and potential established to avoid a significant number of liver biopsies(219). Importantly, in addition several studies have demonstrated the prognostic benefit of measuring levels of

these simple tests for the prediction of adverse liver disease outcomes and death(85, 86, 220-222).

In the largest secondary care cohort (320 NAFLD patients) with a median follow up of 10 years from index liver biopsy, Angulo et al demonstrated that higher results of APRI, BARD score, FIB4 and NFS were associated with significantly increased risk of hepatic decompensation and death(86). NFS was particularly predictive of adverse outcomes, with high risk NFS levels having a hazard ratio of 34.2 for hepatic decompensation and 9.8 for death.

From the NHANES3 cohort in the US, there are also data for the association of these simple fibrosis scores with adverse outcomes in primary care. Kim et al(85), in an analysis of more than 11,000 patients from NHANES3 with a median 14.5 years follow up, showed that whilst an ultrasound diagnosis of NAFLD was not predictive of increased mortality, in the NAFLD patient elevated scores for APRI, FIB4 and NFS predicted mortality (hazard ratios 1.85, 1.66 and 1.69 respectively). Interestingly, increased mortality was explained by excess cardiovascular deaths, rather than liver-related mortality, in these patients. Despite these previous findings, the cross-sectional diagnostic performance of these investigations for liver fibrosis has not yet been published in a primary care setting. Furthermore, based upon the previously published data, these tests represent potential candidate biomarkers which might accurately rule out elevated liver stiffness, and therefore the need to undergo the more expensive TE test.

Although there are large amounts of data to support the use of these simple fibrosis tests in a NAFLD population, the published data to date in alcoholic liver disease have been underwhelming. Understandably, the BARD score and NAFLD fibrosis score have not been studied in ALD as they have been derived as specialist scores for utilisation in patients with NAFLD.

Several studies have investigated APRI, AST:ALT ratio, and FIB4 in hospital-based ALD studies, and shown that their diagnostic performance for predicting significant or advanced liver fibrosis is mediocre to poor(164, 171-173, 223, 224). This may be explained by the fact that these scores both contain at least one of AST level or platelet count in their constituent parts. AST levels are upregulated in increased alcohol intake irrespective of liver fibrosis, and bone marrow toxicity from excessive alcohol use can induce thrombocytopenia. Therefore, the above simple fibrosis tests are likely to overestimate the degree of fibrosis in patients with ALD. However, in a community population where hazardous alcohol use is expected to be of a lower quantity than secondary care ALD populations, these factors may be less impactful and the diagnostic performance of simple tests in ALD improved. Again, like NAFLD, there are currently no published data of the use of these simple fibrosis tests in a community setting of hazardous alcohol use.

A second study of utilising TE in a community setting was therefore performed; investigating patients in an Inner City population using TE alone rather than with a preceding simple fibrosis biomarker step. In combination with the pilot study data from Rushcliffe general practices, this provides a

more generalizable population with which to provide estimates about liver disease diagnoses in primary care using TE. Moreover, the Inner City data utilised alone provide a diagnostic cohort with a single gold standard investigation against which to test simpler fibrosis tests. The aims of this second study were i) to analyse the association of obesity with elevated liver stiffness and cirrhosis in this primary care population, ii) to provide an updated estimate for diagnosed cirrhosis prevalence within this primary care population, and estimates in subgroups of patients with type 2 diabetes or hazardous alcohol use, iii) to analyse the diagnostic performance of simple fibrosis markers for predicting elevated liver stiffness and iv) to assess whether simple fibrosis markers could avoid the need for a significant number of TE scans.

Methodology

Study Setting

This was a cross-sectional study with recruitment from four general medical practices in Nottingham, United Kingdom. The first 2 primary care practices in Rushcliffe, Nottingham have been described in detail in Chapter 3. Following the completion of the pilot study in Rushcliffe, the study was extended to two further primary care practices situated in more deprived boroughs of Inner City Nottingham. These were the Forest Medical Practice in Hyson Green, Nottingham (3,977 adult participants) and the Family Medical Centre in Carlton, Nottingham (6,412 adult participants). TE appointments occurred on Thursday and Friday mornings respectively in these 2 Inner City practices between June 2013 and September 2014.

Therefore, the overall study period for both the Rushcliffe and Inner City practices was 31 months from February 2012 to September 2014.

All 4 practices utilise 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, and 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).

Patient Selection

The inclusion and exclusion criteria for the study have been explained in Chapter 3. As in the Rushcliffe practices, an electronic record search of SystmOne was performed at the commencement of the study to identify those patients with selected risk factors for lifestyle related chronic liver disease. In summary, 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(167) 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.

c) Raised ALT - prospective referrals from participating general practitioners from the 4 studied practices of patients with persistently elevated serum alanine aminotransferase levels (>35IU/L for women, >45IU/L for men), who had neither hazardous alcohol intake nor type 2 diabetes, and negative liver serology for viral, genetic and autoimmune causes of chronic liver disease.

Liver Stiffness Measurement

The methodology for invitation of identified patients to the investigation pathway was the same in Rushcliffe and Inner City practices, and was outlined in Chapter 3. There are, however, two important differences to note between the Rushcliffe and Inner City practices regarding the Transient Elastography (TE) procedure:

i) Serum biomarker utilisation before TE – in the Rushcliffe general practices, a simple serum biomarker test (AST:ALT ratio for hazardous alcohol users and BARD score for type 2 diabetes and raised ALT groups) was used to select those patients who required TE as a second biomarker test. For the Inner City practices, an initial serum biomarker test was not utilised (i.e. eligible patients were invited directly for a TE appointment) for 2 reasons. Firstly, the blood test only excluded 12% of participants from TE whilst also resulting in 60 participants dropping out from the investigation pathway despite abnormal blood biomarker results. Secondly, utilising TE as a single gold standard allowed the analysis of the diagnostic performance of

laboratory tests and simple serum biomarker panels for predicting elevated liver stiffness.

ii) Fasting before TE appointment – towards the end of the pilot Rushcliffe study, new data were published regarding the impact of food and liquid meal ingestion on liver stiffness measurement. In a study of 125 patients with chronic hepatitis C infection, ingestion of a 600kcal test meal resulted in minor but statistically significant elevations in liver stiffness in comparison to fasting baseline results(194). The liver stiffness elevations, felt to result from increased portal blood flow in response to a food challenge, were maximal at 30 minutes but persisted to 2 hours following the test meal ingestion. Similar findings have been shown in subsequent studies(150, 225). As a result, and to reflect local hospital protocol changes for TE measurement, patients were asked to fast for 2 hours prior to liver stiffness measurement in the Inner City practices.

Otherwise, the TE appointment and subsequent follow-up for elevated liver stiffness results was the same in Rushcliffe and Inner City practices as outlined in Chapter 3. The same 3 hospital nurses performed TE scans in all four general practices. Patients with a BMI of <35kg/m^2 underwent TE examination with the FS402 device M probe in the general practice setting. Patients with a BMI>35kg/m^2, and those with an initial failed liver stiffness acquisition using the M probe, underwent TE in the hospital using the FS502 device XL probe. A liver stiffness threshold of 8.0 kilopascals or greater was used to define elevated liver stiffness, and hence clinically significant liver disease. Patients with elevated liver stiffness results, including high but unreliable acquisitions, were reviewed by a visiting consultant hepatologist in

the community. 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 enrolment into cirrhosis surveillance programmes, were organised after this consultation.

Following the TE appointment, patient's electronic primary care records were retrospectively examined to collect recent relevant clinical, anthropometric and laboratory test data. Laboratory tests were only considered if occurring within the 12 months prior to the TE appointment. As fibrosis stage changes take on average 8 years in NAFLD and 5 years in ALD(81, 226) this was felt to be a biologically plausible time in which there were unlikely to be significant changes in a participant's liver stiffness. Laboratory tests were repeated at the time of TE appointment if relevant results were not present from the preceding 12 months. Therefore simple fibrosis marker scores were calculated using laboratory test information from within 1 year of TE scan.

Cirrhosis Diagnoses in Studied Risk Factor Groups

During the study, cirrhosis was diagnosed in all cases based upon TE result in combination with 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 (ALD) if hazardous alcohol use was present in the absence of obesity or type 2 diabetes, as non-alcoholic fatty liver disease (NAFLD) in the presence of type 2 diabetes or obesity, but without hazardous alcohol use, and as dual

aetiology if the combination of hazardous alcohol use and type 2 diabetes or obesity was present.

To evaluate the impact of obesity on the presence of significant liver disease, the percentage of elevated liver stiffness and cirrhosis cases was compared for patients with and without obesity. As waist circumference was not routinely measured, obesity was defined as the presence of body mass index≥30kg/m^2. Subgroup analyses examining patients with hazardous alcohol use, type 2 diabetes and both hazardous alcohol and type 2 diabetes were performed. In view of the differences in study recruitment and TE appointment between general practice locations (additional blood biomarker step in Rushcliffe practices, and fasting TE scans in Inner City practices), a sensitivity analysis was performed using only data from patients recruited from the inner city medical practices.

Considering the new diagnoses of cirrhosis by investigation of the studied risk factor groups, an updated estimate of cirrhosis prevalence was provided for both the entire adult primary care population and patients with type 2 diabetes or hazardous alcohol use. The number and aetiology of cirrhosis diagnoses in the general practice population before study commencement were obtained by searching the electronic patient records. The search algorithm used to identify those patients with pre-existing cirrhosis is shown in Appendix G. The records of patients identified from this electronic search were reviewed to exclude false positive results (e.g. identification of patients with primary biliary cirrhosis (PBC) who had pre-cirrhotic liver fibrosis). Subsequently, for calculation of diagnosed cirrhosis

prevalence at the end of the study period, the number of diagnosed and alive cirrhosis cases known pre-study was added to the new diagnoses during the study period to give the numerator. The total adult patient population in the studied primary care practices (20,868 patients) was the denominator. Pre- and post-study diagnosed cirrhosis were converted to number per 100,000 population with 95% confidence intervals to facilitate comparison with UK cirrhosis prevalence estimates from the General Practice Research Database (GPRD)(20). The referenced work represents the most up to date and thorough UK cirrhosis prevalence estimate in the literature.

For minimum diagnosed cirrhosis prevalence estimates in patients with type 2 diabetes or hazardous alcohol use, the denominator was the total number of patients in the primary care practices identified with the respective risk factor (1,438 patients for hazardous alcohol use and 1,007 patients for type 2 diabetes).

Diagnostic Performance of Simple Serum Tests

Risk Factor Groups

For the analysis of the diagnostic performance of simple fibrosis biomarkers for predicting elevated liver stiffness, only patients who were investigated in the Inner City practices were considered. This was because the simple fibrosis biomarker step utilised in the Rushcliffe practices provided a selection bias as there was in essence not a single gold standard utilised and AST and ALT are found in all of the constituent scores which were analysed further.

As demonstrated in the above introduction section, the diagnostic performance of simple fibrosis markers is vastly different in ALD and NAFLD. In view of this, the studied cohort was split into two groups to assess the diagnostic performance separately in patients with risk factor for these disease states. The two groups were defined as:

1) ALD Risk – this was defined the same as study selection for Hazardous Alcohol use as previously discussed.

2) NAFLD Risk – as in current practice NAFLD is discounted as a diagnosis in the presence of excessive alcohol intake(48), this was defined as patients with type 2 diabetes or raised ALT level who didn't not have a history of hazardous alcohol use in the preceding 5 years prior to TE.

Studied Biomarkers

The diagnostic performance of 5 biomarkers was assessed in the NAFLD Risk group (APRI, AST:ALT ratio, BARD score, FIB4 and NAFLD Fibrosis score (NFS)). As summarised in the introduction section of this chapter these are the simple fibrosis markers which are most validated in secondary care studies of NAFLD and can be calculated from routinely collected laboratory test results found in the general practice electronic database. Only 3 biomarkers (AST:ALT ratio, FIB4 and APRI) were analysed in the hazardous alcohol group as the BARD score and NFS have never been studied previously in ALD. Table 13 lists these investigations, their component parts and formulae for calculation.

The reference standard investigation for the analysis was the presence of liver stiffness ≥8 kilopascals. This was chosen as it both

represents an accurate surrogate marker of significant liver fibrosis from previous secondary care studies, but also the liver stiffness reading which prompted hepatology review in the study. In addition, as only the minority of patients underwent liver biopsy further to consultant hepatologist review, elevated liver stiffness represents the most feasible reference standard in the studied population. Patients were excluded from the analysis if they did not have a valid liver stiffness measurement performed.

Table 13. Simple Fibrosis Biomarkers Analysed For The Prediction of Elevated Liver Stiffness

Index Test	Constituents	Formulae	Validated Cutoffs
APRI	AST, Platelet Count	([**AST**/upper limit of normal of AST]/**Platelet count**[10^9/L]) * 100	0.5, 1, 1.5
AST:ALT Ratio	ALT, AST	AST/ALT	0.8, 1
BARD Score	Body mass index (BMI), AST:ALT ratio,	Weighted Score: -BMI≥28 (1 point) - AST:ALT≥0.8 (2) - Type 2 Diabetes (1)	≥2
FIB4	Age, ALT, AST,	(**Age** [years]*__AST__ [U/L])/(**Platelet Count** [10^9/L] *(**ALT** [U/L])$^{1/2}$)	Low risk: ≤1.3 High risk: ≥2.67
NAFLD Fibrosis Score	Age, Albumin, AST:ALT ratio, Body Mass Index, Platelet Count, Type 2 diabetes (or impaired fasting glucose)	-1.675 + 0.037 * **age** (years) + 0.094 * **BMI** (kg/m2) +1.13 * impaired fasting glycemia or **diabetes** (yes = 1, no = 0) + 0.99 ***AST:ALT ratio** – 0.013 * **platelets** (10^9/L) – 0.66 ***albumin** g/dL)	Low Risk: ≤-1.455 High Risk: ≥0.676

Statistical Analysis

Demographic, anthropometric and laboratory test data were compared between a number of patient groups. This included patients from Rushcliffe and Inner City general practices to highlight their difference in liver disease risk factors. In addition comparisons were performed between non-obese and obese patients within the hazardous alcohol and type 2 diabetes risk factor groups and between patients with normal liver stiffness and elevated liver stiffness/cirrhosis.

The impact of obesity on liver disease diagnoses was analysed by comparing cirrhosis and elevated liver stiffness prevalence between obese and non-obese participants. This analysis was performed separately for patients with hazardous alcohol use, type 2 diabetes and both of these risk factors.

Diagnostic statistical analyses were performed in which the diagnostic performance of simple fibrosis markers for the prediction of elevated liver stiffness was evaluated. This included evaluation of previously validated thresholds for these markers for ALD and NAFLD from the secondary care literature.

Lastly, an analysis was performed to determine how many TE scans could be saved by utilising simple fibrosis markers and simple laboratory tests to select patients requiring TE. The previously discussed simple fibrosis biomarkers were analysed, in addition to simple laboratory tests and body mass index which have plausibility for predicting elevated liver stiffness from the pilot Rushcliffe study (Chapter 3, table 11).

Statistical analysis was performed using Stata version 13.1 (StataCorp LP). Categorical data are presented as number (percentage). The Shapiro-Wilk test was performed on all continuous variables to determine whether the data were parametric or non-parametric. A Shapiro-Wilk p value≤0.05 indicates that the data are non-parametric (not normally distributed). Subsequently, continuous data are presented as mean (standard deviation (SD)) for normally distributed data, and medians (range) for non-normally distributed data. Two sample t test was used for normally distributed variables and Mann-Whitney test for not normally distributed variables. Categorical variables were compared using chi-squared test, or Fisher's exact test if any of the groups in the 2x2 table had fewer than 10 participants present.

For analyses evaluating the impact of obesity on elevated liver stiffness and cirrhosis diagnoses, odds ratios and 95% confidence intervals are reported comparing patients with and without obesity.

For diagnostic statistical analyses, receiver operated characteristic (ROC) curves were first created for the prediction of elevated liver stiffness by the candidate simple fibrosis markers. Subsequently the area under the ROC curve (AUROC) was calculated. The AUROC provides an estimate of global diagnostic performance across the full range of its possible values in the studied cohort. AUROCs are displayed with 95% confidence intervals for the studied index tests to facilitate comparison of diagnostic performance. A perfect index test, which has both a sensitivity and specificity of 100% for the target condition produces an AUROC of 1. In imperfect tests, as seen

frequently in clinical practice, an AUROC of ≥0.9 represents excellent diagnostic performance, an AUROC of 0.8-0.9 good diagnostic performance and 0.7-0.8 satisfactory performance. However, further examination of diagnostic performance is required. In the current primary care setting for example, the hypothesised role of the simple fibrosis markers is to exclude elevated liver stiffness and therefore the sensitivity and negative predictive values of the studied markers will be the most important diagnostic characteristic. Therefore, using validated threshold values for liver fibrosis previously derived in secondary care studies of ALD and NAFLD, a range of diagnostic statistics were calculated (sensitivity, specificity, positive and negative predictive values and diagnostic odds ratio).

To evaluate the number of TE examinations which would be saved, diagnostic sensitivities of 90% and 100% for elevated liver stiffness were calculated for the candidate variables. A sensitivity of 100% means that no cases of elevated liver stiffness would be missed. A sensitivity of 90% ensures that a small number of cases of elevated liver stiffness (10%) are missed, which would be considered an acceptable trade-off if a significant number of TE scans are avoided.

Ethical Approval

Discussion of the ethical considerations for performing TE in the primary care practices was outlined in Chapter 3. Subsequently, local regulatory approval was obtained from the Leicester Research Ethics Committee in May 2013 prior to the Inner City study phase (study identification 13/EM/0123) to recruit participating patients to a longitudinal

cohort of those who had undergone TE as part of the community study. Consent for the cohort did not cover cross sectional data use as part of service evaluation, but rather longitudinal analysis of future primary care record data, contact for qualitative interview (chapter 5) and approach for future related research studies. In agreeing patients, written informed consent for the longitudinal cohort was gained during the TE appointment in Inner City patients, whilst Rushcliffe patients were retrospectively contacted by post.

Results

Study Population

The total adult population in the studied primary care centres at commencement of the study was 20,868 patients. Table 14 shows the characteristics of patients in all 4 participating general practices, and compares those patients from Rushcliffe and Inner City general practices. The most striking difference between general practice sites was body mass index categories; the number of overweight (40.2% vs. 21.7%; $p<0.001$) and obese (24.3% vs.12.6%; $p<0.001$) patients was significantly higher in Inner City practices.

Overall in all 4 practices comprising the study population, hazardous alcohol use was detected in 1,438 patients (6.9%) and type 2 diabetes in 1,007 patients (4.8%). When comparing general practice location, the Inner City practices had a significantly higher prevalence of hazardous alcohol use (7.5% vs. 6.3%; $p<0.001$) and type 2 diabetes (5.9% vs. 3.7%; $p<0.001$) than

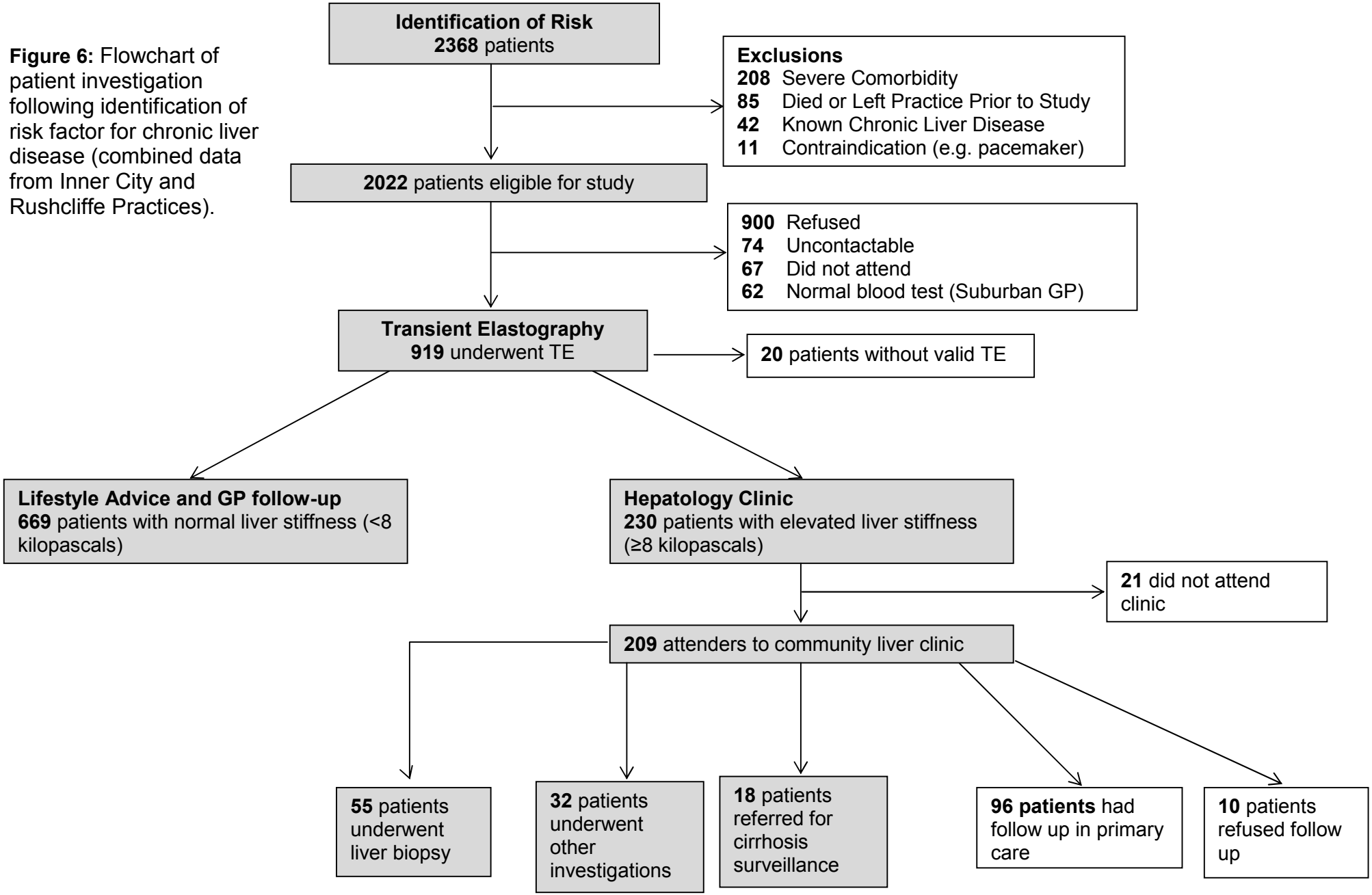
Rushcliffe practices. There were 2,368 patients with one or more of hazardous alcohol use or type 2 diabetes identified from the electronic patient record search, of whom 346 were subsequently excluded (see Figure 6).

Subsequently 919/2,022 patients (45.4%) attended the TE appointment; 401 patients (43.6%) had hazardous alcohol use, 554 patients (60.3%) had type 2 diabetes (including 65 patients (7.1%) with both risk factors present), and 29 (3.2%) 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-attendees, TE appointment attendees were significantly less likely to be hazardous alcohol users (43.6% vs. 83.0%; $p<0.001$), significantly more likely to have type 2 diabetes (60.3% vs. 20.2%; $p<0.001$), 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; $p<0.001$).

Table 14. Baseline characteristics of total adult patient population at studied General Practice (GP) sites				
Variable	**All Adult GP Patients (n=20,868)**	**Rushcliffe Patients (n=10,479)**	**Inner City Patients (n=10,389)**	**P Value**
Age (n%)				
- 18-30 years	4730 (22.7%)	2100 (20.4%)	2640 (25.4%)	**<0.001**
- 31-40 years	4802 (23.0%)	2469 (23.6%)	2333 (22.5%)	0.06
- 41-50 years	3889 (18.6%)	1903 (18.2%)	1986 (19.1%)	0.08
- 51-60 years	2866 (13.7%)	1331 (12.7%)	1535 (14.8%)	**<0.001**
- 61-70 years	2240 (10.7%)	1287 (12.3%)	953 (9.2%)	**<0.001**
- 71-80 years	1387 (6.6%)	781 (7.5%)	606 (5.8%)	**<0.001**
->80 years	954 (4.6%)	608 (5.8%)	346 (3.3%)	**<0.001**
Male Gender n(%)	10522 (50.4%)	5131 (49.0%)	5391 (51.2%)	**<0.001**
Body Mass Index n(%)				
- 25-29.9	6912 (33.1%)	2835 (27.1%)	4177 (40.2%)	**<0.001**
- ≥30	3828 (18.3%)	1320 (12.6%)	2527 (24.3%)	**<0.001**
- Missing values	2358 (11.3%)	1363 (13.0%)	995 (9.6%)	**<0.001**
Hazardous Alcohol Use n(%)	1438 (6.9%)	658 (6.3%)	780 (7.5%)	**<0.001**
Type 2 Diabetes n(%)	1007 (4.8%)	390 (3.7%)	617 (5.9%)	**<0.001**
Ischaemic Heart Disease n(%)	829 (4.0%)	423 (4.0%)	406 (3.9%)	0.66
Hypertension n(%)	2877 (13.8%)	1521 (14.5%)	1356 (13.1%)	**0.002**
Hyperlipidaemia n(%)	3923 (18.8%)	2117 (20.2%)	1806 (17.4%)	**<0.001**

P value compares patients from Rushcliffe primary care practices and Inner City practices; p values≤0.05 are statistically significant and are displayed in bold.

Figure 6: Flowchart of patient investigation following identification of risk factor for chronic liver disease (combined data from Inner City and Rushcliffe Practices).



Transient Elastography Results

Successful liver stiffness results were obtained in 899 patients (97.8% of those undergoing TE) who were included in the subsequent analyses. 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 at the hospital setting. Unreliable liver stiffness acquisitions occurred in 44 patients (4.9%).

The clinical data of all patients with valid TE measurements, and subgroups of patients with hazardous alcohol use and type 2 diabetes, comparing obese and non-obese individuals, is shown in table 15. Obesity was present in 96/386 (24.9%) of hazardous alcohol users and 273/541 (50.5%) of patients with type 2 diabetes. Median liver stiffness values were significantly higher amongst both obese patients with hazardous alcohol use (median 6.35kPa vs. 5.1 kPa; $p<0.001$) and obese patients with type 2 diabetes (median 7.1 kPa vs. 5.7 kPa; $p<0.001$) than non-obese patients. Moreover, obese patients were more likely to have raised ALT levels in both hazardous alcohol use (22.9% vs. 5.5%; $p<0.001$) and type 2 diabetes (18.3% vs. 9.0%; $p<0.001$) groups.

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 and 40% of obese patients. Amongst these patients, on further testing a single case of primary biliary cholangitis in a patient with coexistent NASH was identified.

Table 15. Characteristics of 899 patients with successful TE, and comparing obese and non-obese patients with hazardous alcohol use and type 2 diabetes					
Variable	**All Study Patients (n=899)**	**Hazardous Alcohol and Not Obese (n=290)**	**Hazardous Alcohol and Obese (n=96)**	**Type 2 Diabetes and Not Obese (n=268)**	**Type 2 Diabetes and Obese (n=273)**
Age (years)	61 (49-70)	54 (42-64)	59.5 (51-67)*	66 (56-75)	63 (55-71)$
Male Gender n(%)	592 (65.9%)	219 (75.5%)	81 (84.4%)	170 (63.4%)	166 (60.8%)
Ethnicity					
- Caucasian	750 (83.4%)	267 (92.1%)	91 (92.8%)	190 (70.9%)	237 (86.8%)$
- Asian	66 (7.3%)	5 (1.7%)	0 (0%)	41 (15.3%)	16 (5.9%)$
- Black	62 (6.9%)	13 (81.3%)	3 (3.1%)	29 (10.8%)	16 (5.9%)$
- Other	21 (2.3%)	5 (1.7%)	2 (2.1%)	8 (3.0%)	4 (1.5%)
Body Mass Index (kg/m^2)	28.3 (25.0-32.3)	24.9 (22.3-26.9)	33.0 (31.1-35.6)*	26.6 (24.5-28.3)	33.9 (31.5-37)$
Obesity n(%)	350 (38.9%)	0 (0%)	96 (100%)*	0 (0%)	273 (100%)$
Type 2 Diabetes (n(%)	543 (60.4%)	34 (11.7%)	30 (32.3%)*	268 (100%)	273 (100%)
Hazardous Alcohol Use (n(%)	391 (43.5%)	290 (100%)	96 (100%)	34 (12.7%)	30 (11.0%)
Alcohol intake (units/week)	6 (0-28)	30 (23-50)	28 (20-40)	0 (0-6)	1 (0-7)
Raised ALT (%)	161 (17.9%)	45 (15.5%)	22 (22.9%)	24 (9.0%)	50 (18.3%)$
Ischaemic Heart Disease n(%)	108 (12.0%)	14 (4.8%)	14 (14.6%)	37 (13.8%)	48 (17.6%)
Hypertension n(%)	396 (44.1%)	66 (22.8%)	49 (51.0%)*	134 (50.0%)	177 (64.8%)$
Metabolic Syndrome n(%)	288 (32.0%)	0 (0%)	48 (50%)*	11 (4.1%)	255 (93.4%)$
Liver Stiffness Median (kPa)	5.8 (4.5-8.1)	5.1 (4.2-6.2)	6.35 (4.8-9.4)*	5.7 (4.4-7.3)	7.1 (5.4-10.9)$

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 chi-squared test. P values reaching statistical significance (p≤0.05) are shown in bold. *=p value <0.05 comparing hazardous alcohol users who are non-obese and obese, $ = p value <0.05 comparing type 2 diabetics who are non-obese and obese. ALT = alanine aminotransferase (raised ALT = >35U/l for women and >45U/l for men), kPa = kilopascals

Cirrhosis Diagnoses

In total, 209 patients attended and were reviewed in hepatology clinics and 27 of these were newly diagnosed with cirrhosis during the study period (3% of valid TE results). Relevant clinical characteristics of these patients are displayed in Appendix F. Cirrhosis aetiologies were NAFLD in 16 patients (59.3% of newly detected cirrhosis), ALD 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 patient 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 higher BMI values (33.2 vs. 27.4; p=<0.001), and greater prevalence of metabolic syndrome (59.3% vs. 25.5%; p=0.003) but no significant differences in hazardous alcohol use or type 2 diabetes were seen (see Table 16). Normal ALT values were found in 66.7% of patients with cirrhosis.

Prior to study commencement, there were 23 diagnosed cases of cirrhosis in the population of the studied general practices. Cirrhosis aetiologies were ALD (14 patients), Hepatitis B or C (5), NAFLD (1) and other (3). This equates to a pre-study diagnosed cirrhosis prevalence of 110.2 cases per 100,000 population (95% CI 65.2-155.2). Following the study there were 50 diagnosed cirrhosis cases, equating to an estimated cirrhosis prevalence of 239.6 cases per 100,000 (95% CI 173.3-305.9) in the adult primary care population. Overall, 20 of 1,007 known patients with type

2 diabetes in the studied general practices (2%), and 25 of 1,438 known hazardous alcohol drinkers (1.7%) were diagnosed with cirrhosis at the end of the study.

Table 16. Clinical characteristics of 899 patients with successful TE, comparing patients with normal liver stiffness (n=669) with patients with elevated liver stiffness (n=230) and 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
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
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**

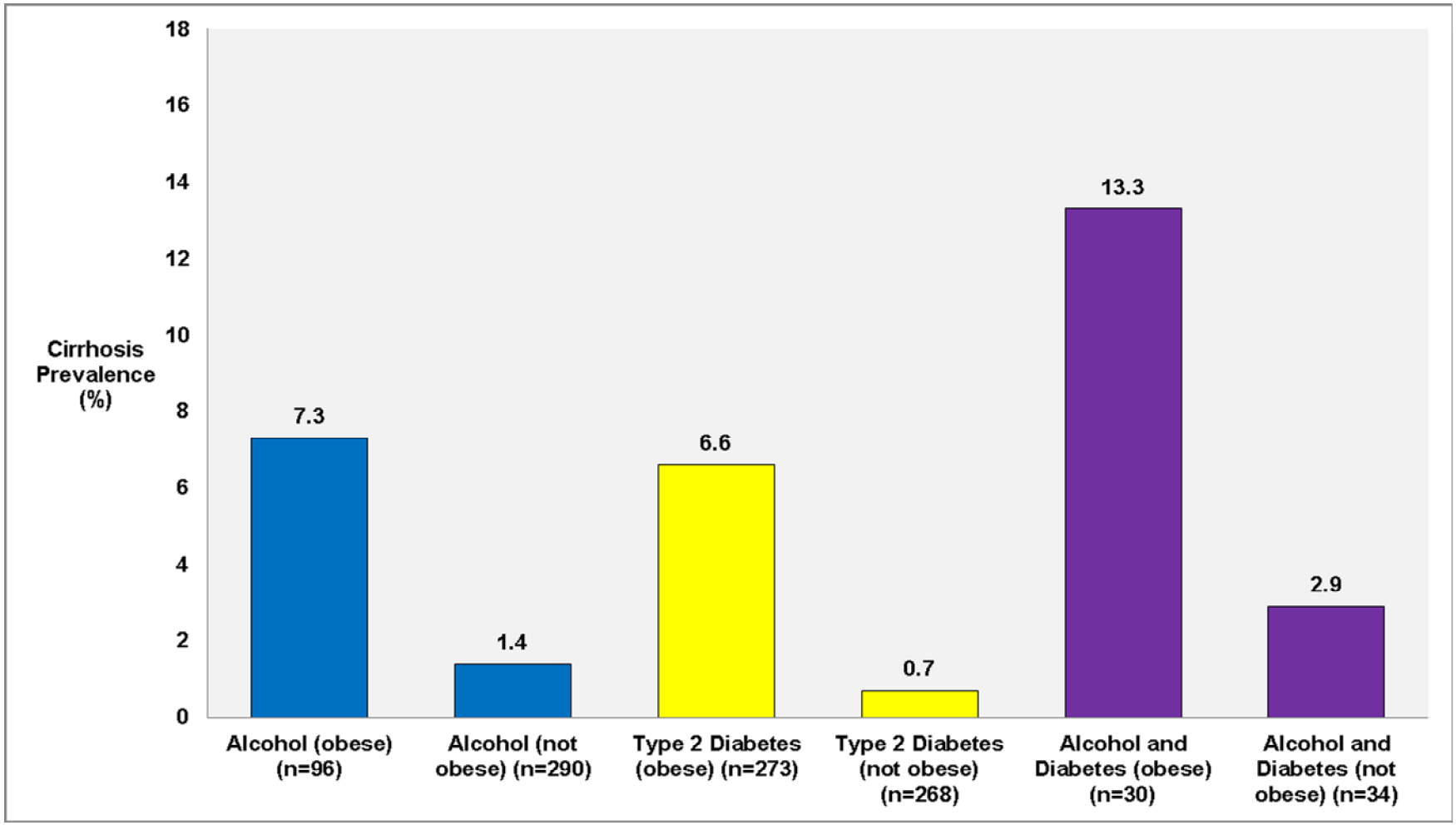
Normally distributed numerical variables are displayed as mean (standard deviation(SD)) and compared using the t test, non-normally distributed numerical variables are displayed as median(interquartile range) and compared using the Mann-Whitney test. Categorical variables are displayed as n(%) and compared 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.

Impact of Obesity on Elevated Liver Stiffness and Cirrhosis Diagnoses

Obesity was present in 140/230 (60.9%) of patients with elevated liver stiffness and 22/27 (81.5%) of patients with cirrhosis. Hazardous alcohol users with obesity were significantly more likely to be diagnosed with cirrhosis than non–obese patients (odds ratio 5.6; 95% CI 1.6-19.7; cirrhosis prevalence 7.3% vs. 1.4%), as were patients with type 2 diabetes and obesity (odds ratio 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%.(see Figure 7). Elevated liver stiffness prevalence was significantly higher in obese hazardous alcohol users (odds ratio 3.1; 95% CI 1.8-5.3%; elevated liver stiffness prevalence 34.4% vs. 14.5%) and obese patients with type 2 diabetes (odds ratio 2.9; 95% CI 1.9-4.2; 42.5% vs. 20.6%), but was not significantly higher in patients with both hazardous alcohol use and type 2 diabetes (odds ratio 2.1; 95% CI 0.8-5.9; 46.7% vs. 29.4%) (see Figure 8).

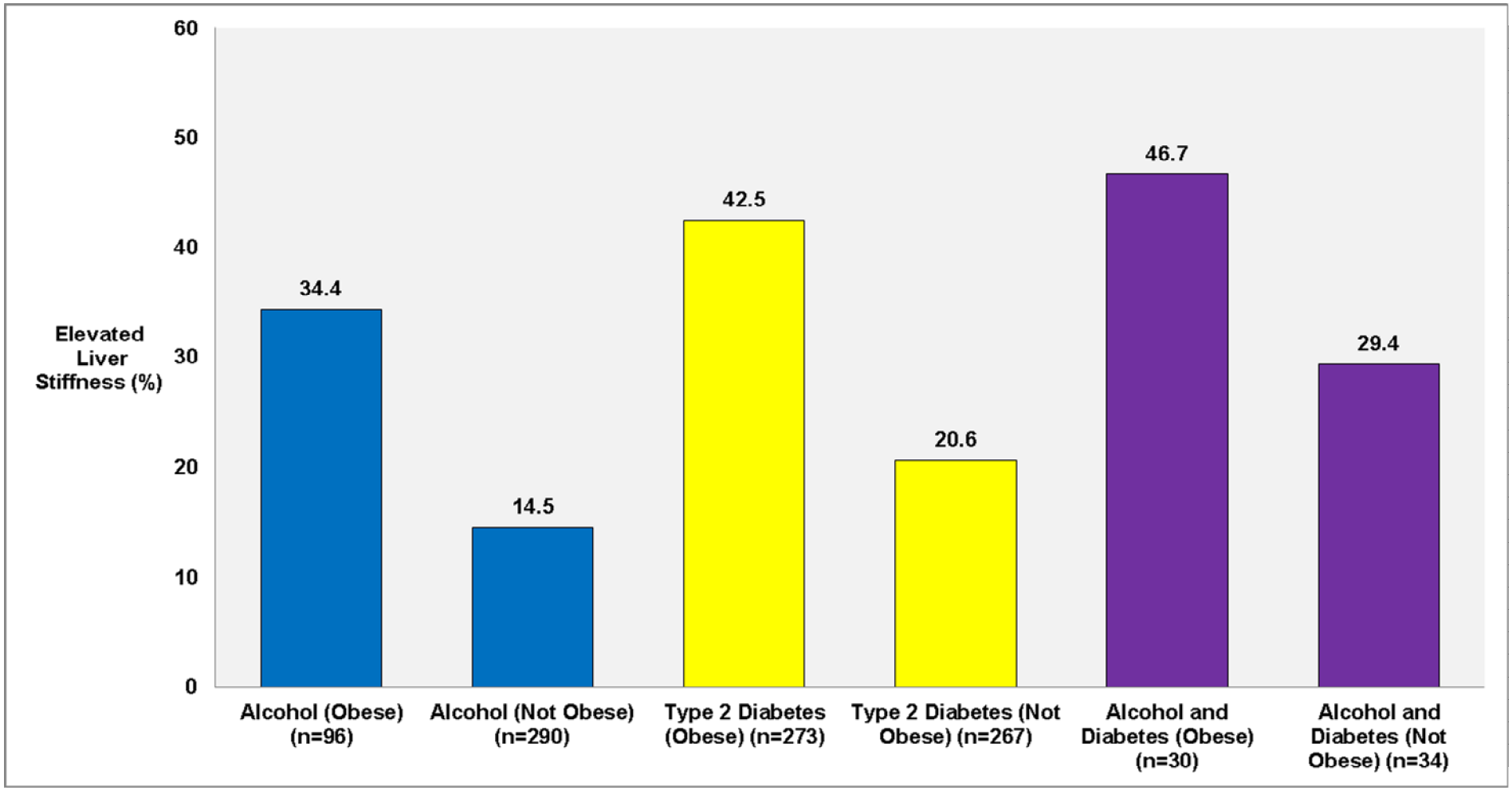
Estimates of the impact of obesity on cirrhosis and elevated liver stiffness diagnoses were similar in the sensitivity analysis considering only patients from inner city practices. Odds ratios comparing obese and non-obese patients for cirrhosis diagnoses were all statistically significant; 3.4 (95% CI 1.7-6.7) for hazardous alcohol use, 3.7 (95% CI 2.2-6.1) for type 2 diabetes and 3.8 (95% CI 1.1-13.7) for patients with both hazardous alcohol use and type 2 diabetes. Odds ratios for elevated liver stiffness were 3.1 (95% CI 0.8-11.8) for hazardous alcohol, 3.8 (95% CI 0.8-18.1) for type 2 diabetes and 2.9 (0.3-29.8) for patients with both type 2 diabetes and hazardous alcohol.

Figure 7: Comparison of cirrhosis prevalence in obese and non-obese patients with hazardous alcohol use, type 2 diabetes and a combination of both risk factors.



Odds Ratio (95% CI)	**5.6 (1.6-19.7)**	**9.4 (2.2-40.9)**	**5.1 (0.5-48.2)**

Figure 8: Comparison of elevated liver stiffness prevalence in obese and non-obese patients with hazardous alcohol use, type 2 diabetes and a combination of both risk factors.



Odds Ratio (95% CI)	**3.1 (1.8-5.3)**	**2.9 (1.9-4.2)**	**2.1 (0.8-5.9)**

Diagnostic Statistics

The following analyses were performed on patients attending for TE appointments in the Inner City primary care practices. Overall, 541 patients attended for TE of which 501 scans (92.6%) occurred at the primary care practices and the remaining 40 occurred at the hospital using the XL probe. Successful liver stiffness measurements were possible in 532 patients (98.3%); unreliable liver stiffness measurements were obtained in an additional 20 patients (3.8% of those with successful TE).

The baseline clinical characteristics of the 532 patients with successful liver stiffness measurement are shown in Table 17. Median age of participants was 58.5 years (IQR 48-67 years) and 345 participants (64.9%) were male. Elevated liver stiffness measurements (≥8 kilopascals) were obtained in 132 patients (24.8%).

Overall, 223 patients were found to have hazardous alcohol use recorded within the previous 5 years and made up the ALD risk group, whilst the remaining 309 patients made up the NAFLD risk group. There were a number of statistically significant differences between the ALD and NAFLD risk groups. Of note, the NAFLD risk group were significantly older (median age 61.0 years vs. 56.0 years; $p<0.001$), were more likely to be female (male gender 56.3% vs. 76.7%; $p<0.001$), had larger body mass index readings (median BMI 30.1 vs. 26.3; $p<0.001$), higher liver stiffness readings (median TE result 6.2kPa vs. 5.3kPa; $p<0.001$) and a higher percentage of patients with elevated liver stiffness (28.5% vs. 19.7%; $p=0.02$).

Table 17. Baseline characteristics of 532 Inner City primary care patients undergoing TE, and comparing ALD and NAFLD risk				
Variable	**All Study Patients (n=532)**	**ALD Risk (n=223)**	**NAFLD Risk* (n=309)**	**P Value**
Age (years)	58.5 (48.0-67.0)	56.0 (45.0-55.0)	61.0 (52.0-69.0)	**<0.001**
Male Gender n(%)	345 (64.9%)	171 (76.7%)	174 (56.3%)	**<0.001**
Ethnicity				**<0.001**
- Caucasian	416 (78.2%)	204 (91.5%)	212 (68.6%)	
- Asian	46 (8.7%)	1 (0.5%)	45 (14.6%)	
- Black	58 (10.9%)	16 (7.2%)	42 (13.6%)	
- Other	12 (2.3%)	2 (0.9%)	10 (3.2%)	
Body Mass Index (kg/m^2)	28.7 (25.2-33.0)	26.3 (23.0-31.1)	30.1 (26.6-34.3)	**<0.001**
Alcohol intake (units/week)	4 (0-28)	30 (21-50)	0 (0-2)	**<0.001**
Type 2 Diabetes n(%)	338 (63.5%)	45 (20.2%)	293 (94.8%)	**<0.001**
Ischaemic Heart Disease n(%)	57 (10.7%)	19 (8.5%)	38 (12.3%)	0.20
Hypertension n(%)	229 (43.1%)	72 (32.3%)	157 (50.8%)	**<0.001**
Hyperlipidaemia n(%)	368 (69.2%)	104 (46.6%)	264 (85.4%)	**<0.001**
Metabolic Syndrome	176 (33.1%)	33 (14.8%)	143 (46.3%)	**<0.001**
Liver Stiffness Median (KPA)	5.7 (4.5-7.95)	5.3 (4.3-6.7)	6.2 (4.9-8.6)	**<0.001**
Elevated Liver Stiffness (≥8kPa) n(%)	132 (24.8%)	44 (19.7%)	88 (28.5%)	**0.02**

*NAFLD risk defined as type 2 diabetes, or raised serum ALT level with metabolic risk factors. Normally distributes numerical variables are displayed as mean (standard deviation(SD)) and compared using two sample T-test; non-normally distributed numerical variables are displayed as median (interquartile range) and compared using Mann-Whitney U test; categorical variables are displayed as n(%) and compared using Chi-Squared test. P values compare ALD risk and NAFLD risk groups. P value ≤0.05 demonstrates statistical significance (bold).

Table 18: Biochemical and Clinical Features of Patients with ALD Risk and NAFLD Risk Comparing Normal and Elevated Liver Stiffness						
	ALD Risk (n=223)			NAFLD Risk (n=309)		
Variable	**Normal Liver Stiffness (n=179)**	**Elevated Liver Stiffness (n=44)**	**P Value**	**Normal Liver Stiffness (n=221)**	**Elevated Liver Stiffness (n=88)**	**P Value**
Age (Years)	55 (44-64)	58.5 (48.5-65)	0.27	61 (52-69)	61.5 (47.5-69)	0.75
Male - n(%)	133 (74.3%)	38 (86.4%)	0.09	122 (55.2%)	52 (59.1%)	0.53
Body Mass Index (g/m^2)	25.6 (22.5-30.1)	31.7 (27.1-34.9)	**<0.001**	28.8 (26.0-32.1)	34.1 (29.8-37.3)	**<0.001**
Alcohol Intake - units/week	30 (20-50)	40 (24-60)	0.11	0 (0-2)	0 (0-2)	0.52
Metabolic Syndrome n(%)	19 (10.6%)	14 (31.8%)	**<0.001**	87 (39.3%)	56 (36.4%)	**<0.001**
Ischaemic Heart Disease n(%)	13 (7.3%)	6 (13.6%)	0.18	25 (11.3%)	13 (14.8%)	0.40
Platelet Count (10^9/L)	251 (220-286.5)	240.5 (187.5 – 294)	0.32	261 (222-313.5)	251 (220-294)	0.19
ALT (U/L)	24 (18-37.5)	32 (22.5-50.5)	**0.01**	21 (16-29)	31 (21-47.5)	**<0.001**
AST (U/L)	26 (22-35)	32 (21-57.5)	**0.04**	21 (18-25)	25 (20-35)	**<0.001**
Bilirubin (µmol/L)	9 (8-12)	10.5 (9-14)	**0.04**	8 (7-11)	9 (6.5-11)	0.92
Albumin (g/L)	38.7 (3.4)	37.8 (3.1)	0.09	38.2 (3.2)	38.2 (3.4)	0.998
AST:ALT Ratio	1.06 (0.89-1.36)	1.05 (0.89-1.46)	0.78	0.96 (0.79-1.18)	0.85 (0.71-1.08)	**<0.001**
APRI	0.30 (0.24-0.42)	0.41 (0.24-0.71)	**0.02**	0.22 (0.18-0.31)	0.28 (0.20-0.45)	**<0.001**

FIB4	1.21 (0.87-1.625)	1.50 (1.01-2.325)	**0.03**	1.04 (0.795-1.42)	1.07 (0.78-1.5)	0.40
NAFLD Fibrosis Score	------	------	----	-0.498 (-1.416 – 0.345)	-0.118 (--1.197 – 0.625)	**0.02**

Normally distributes numerical variables are displayed as mean (standard deviation(SD)) and compared using two sample T-test; non-normally distributed numerical variables are displayed as median (interquartile range) and compared using Mann-Whitney U test; categorical variables are displayed as n(%) and compared using Chi-Squared test or Fishers Exact Test. ALT = alanine aminotransferase, AST = aspartate aminotransferase. P values reaching statistical significance ($p \leq 0.05$) are shown in bold. Missing values (ALD Risk): BMI (n=6), Alcohol intake (2), ALT (3), AST (3), Bilirubin (3), Albumin (3), Platelet Count (7), AST:ALT ratio (3), APRI (7), FIB4 (7). Missing values (NAFLD risk): BMI (n=2), Alcohol intake (3), ALT (0), AST (0), Bilirubin (0), Albumin (0), Platelet Count (10), AST:ALT ratio (0), APRI (10), FIB4 (10).

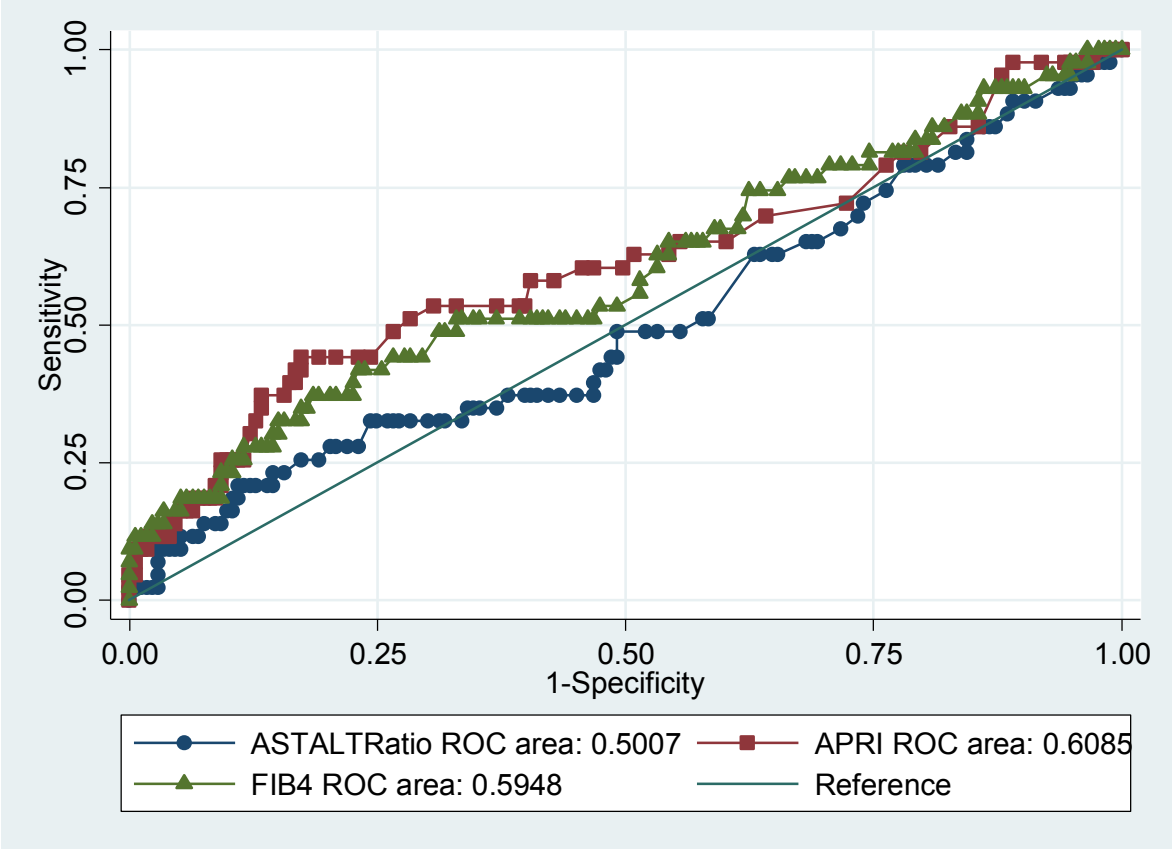
ALD Risk Group

Of the 223 patients analysed in the ALD risk group, elevated liver stiffness was found in 44 patients (19.7%). Regarding clinical and anthropometric features, patients with elevated liver stiffness had significantly higher body mass index values (median BMI 31.7 vs. 25.6; $p<0.001$) and higher prevalence of metabolic syndrome (31.8% vs. 10.6%; $p<0.001$) (see Table 18). Regarding laboratory results, patients with elevated liver stiffness had significantly higher levels of ALT (32 vs. 24; p=0.01), AST (32 vs. 26; p=0.04) and bilirubin (10.5 vs. 9; p=0.04). Moreover, median APRI levels (0.40 vs. 0.30; p=0.02) and FIB4 levels (1.50 vs. 1.21; were significantly higher in patients with elevated liver stiffness, but AST:ALT levels were no different.

Simple Fibrosis Markers

Receiver operated characteristic (ROC) curves for the prediction of elevated liver stiffness in the ALD risk group are shown in Figure 9:

Figure 9: Receiver Operated Characteristic Curves of Simple Fibrosis Markers for the Prediction of Elevated Liver Stiffness in 223 patients with ALD risk



The diagnostic performance of all 3 simple fibrosis markers was mediocre to poor for the prediction of elevated liver stiffness in patients with ALD risk. Area under the ROC curve for AST:ALT ratio was 0.501 (95%CI 0.398-0.603), for APRI was 0.609 (95%CI 0.504-0.713) and for FIB4 was 0.595 (0.493-0.697). At validated cutoffs from previous secondary care studies, diagnostic statistics for the prediction of elevated liver stiffness in ALD risk are shown in table 19. Negative predictive values for studied cutoff values for all 3 simple fibrosis markers were similar (range 80.5% to 85.1%). However sensitivities and specificities varied markedly between the 3 tests. AST:ALT ratio was the most sensitive test for identifying elevated liver stiffness (sensitivities 86% at cutoff value of 0.8 and 62.8% at cutoff value of 1.0), but also the least specific (specificities 14.1% at cutoff value of 0.8 and 37.3% at cutoff value of 1.0). Positive predictive values for all tests were poor (range 19.6% (AST:ALT ratio) to 41.7% (APRI cutoff 1.5)).

Table 19. Diagnostic Performance of Validated Cutoffs of Serum Fibrosis in the Prediction of Elevated Liver Stiffness Due to Alcoholic Liver Disease (n=223)								
Variable	**Cut-off**	**AUROC (95%CI)**	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**DOR**	**Accuracy**
AST:ALT Ratio	0.8	0.501 (0.398-0.603)	86.0%	14.1%	19.6%	80.6%	1.01	28.2%
AST:ALT Ratio	1	0.501 (0.398-0.603)	62.8%	37.3%	19.6%	80.5%	1.00	42.3%
APRI	0.5	0.609 (0.504-0.713)	41.9%	82.7%	37.5%	85.1%	3.43	74.5%
APRI	1	0.609 (0.504-0.713)	18.6%	93.1%	40.0%	82.1%	3.07	78.2%
APRI	1.5	0.609 (0.504-0.713)	11.6%	96.0%	41.7%	81.4%	3.12	79.2%
FIB4	1.3	0.595 (0.493-0.697)	51.2%	56.1%	22.4%	82.2%	1.34	55.1%
FIB4	2.67	0.595 (0.493-0.697)	18.6%	93.1%	40.0%	82.1%	3.07	78.2%

AUROC = area under the receiver operated characteristic curve, DOR = diagnostic odds ratio, NPV = negative predictive value, PPV = positive predictive value

Reducing need for TE scans

Diagnostic thresholds for laboratory tests and body mass index which would have a 100% and 90% sensitivity for elevated liver stiffness were derived (see table 20). Subsequently, the number of TE scans which would be avoided at these thresholds is shown.

Table 20. Utilisation of Transient Elastography At High Sensitivity Cutoffs of Index Tests for the Prediction of Clinically Significant Alcoholic Liver Disease (n=223)				
Variable	**100% Sensitive Cut-off**	**Transient Elastography Saved (%)**	**90% Sensitive Cut-off**	**Transient Elastography Saved (%)**
BMI (kg/m^2)	16.6	1 (0.5%)	25.0	83 (38.2%)
Platelet Count (10^9/L)	468	2 (0.9%)	325	26 (11.8%)
ALT (U/L)	9	2 (0.9%)	15	25 (9.1%)
AST (U/L)	15	4 (1.8%)	18	18 (8.2%)
Bilirubin (µmol/L)	4	3 (1.4%)	7	26 (11.8%)
Albumin (g/L)	44	5 (2.3%)	42	25 (9.1%)
AST:ALT Ratio	0.49	1 (0.5%)	0.75	23 (10.5%)
APRI	0.12	2 (0.9%)	0.19	23 (10.5%)
FIB4	0.51	6 (2.8%)	0.72	29 (13.4%)

ALT = alanine aminotransferase, AST = aspartate aminotransferase, BMI = Body mass index

At cutoffs which were 100% sensitive for predicting elevated liver stiffness, only a significant minority of TE scans would be avoided (range 0.5%-2.8%). At cutoffs which were 90% sensitive for predicting elevated liver stiffness, a larger percentage TE scans would have been avoided (range 8.2%-38.2%). In the Rushcliffe pilot 11.9% of patients refused scan appointments following a simple fibrosis biomarker test. In the Inner City practices only 2 variables would avoid a greater number of TE scans than this whilst retaining a 90% sensitivity for elevated liver stiffness; a FIB4 cutoff

of 0.72 would have avoided 13.4% of TE scans and a BMI cutoff of 25.0 would have avoided 38.2% of TE scans. Furthermore, body mass index produced an area under the ROC curve of 0.730 (95%CI 0.644-0.817) for predicting elevated liver stiffness. The body mass index cutoff of 25.0 had a sensitivity of 90.5%, specificity of 45.1%, positive predictive value of 28.4% and negative predictive value of 95.2% for detecting elevated liver stiffness.

NAFLD Risk Group

Of the 309 patients with NAFLD risk, elevated liver stiffness was found in 88 patients (28.5%). Regarding clinical and anthropometric features, patients with elevated liver stiffness had significantly higher body mass index (median BMI 34.1 vs. 28.8; p<0.001) and higher metabolic syndrome prevalence (63.6% vs. 39.3%; p<0.001). Regarding laboratory test results, patients with elevated liver stiffness had significantly higher median ALT levels (31 vs. 21; p<0.001) and AST levels (25 vs. 21; p<0.001). Median APRI levels (0.28 vs. 0.22; p<0.001) and NAFLD fibrosis score levels (-0.118 vs. -0.498; p=0.02) were also significantly higher in patients with elevated liver stiffness. FIB4 levels were not statistically different, AST:ALT ratio levels were significantly lower in patients with elevated liver stiffness (0.85 vs. 0.96; p<0.001).

Simple Fibrosis Markers

Receiver operated characteristic (ROC) curves for the prediction of elevated liver stiffness in the NAFLD risk group are shown in Figure 10. The overall diagnostic performance of all 5 markers was mediocre to poor. AUROC for AST:ALT ratio was 0.380 (95% CI 0.309-0.452), for APRI was 0.635 (95% CI 0.566-0.704), for BARD score was 0.540 (95% CI 0.466-0.614), for FIB4 was 0.531 (95% CI 0.457-0.605) and for NAFLD fibrosis score was 0.590 (95% CI 0.517-0.662).

At validated cutoffs from previous secondary care studies, diagnostic statistics for the prediction of elevated liver stiffness in NAFLD risk patients are shown in table 21. In all cases the negative predictive values for elevated liver stiffness were inadequate (range 64.4% to 76.9%). The most sensitive test cutoffs for elevated liver stiffness were BARD score (score ≥2 had a sensitivity of 92%) and the low risk threshold of NFS (score -1.455 had a sensitivity of 82.6%). Both of these thresholds, however, were associated with low specificities for elevated liver stiffness (9.6% for BARD score and 23.7% for NFS).

Figure 10: Receiver Operated Characteristic Curves of Simple Fibrosis Markers for the Prediction of Elevated Liver Stiffness in 309 patients with NAFLD risk

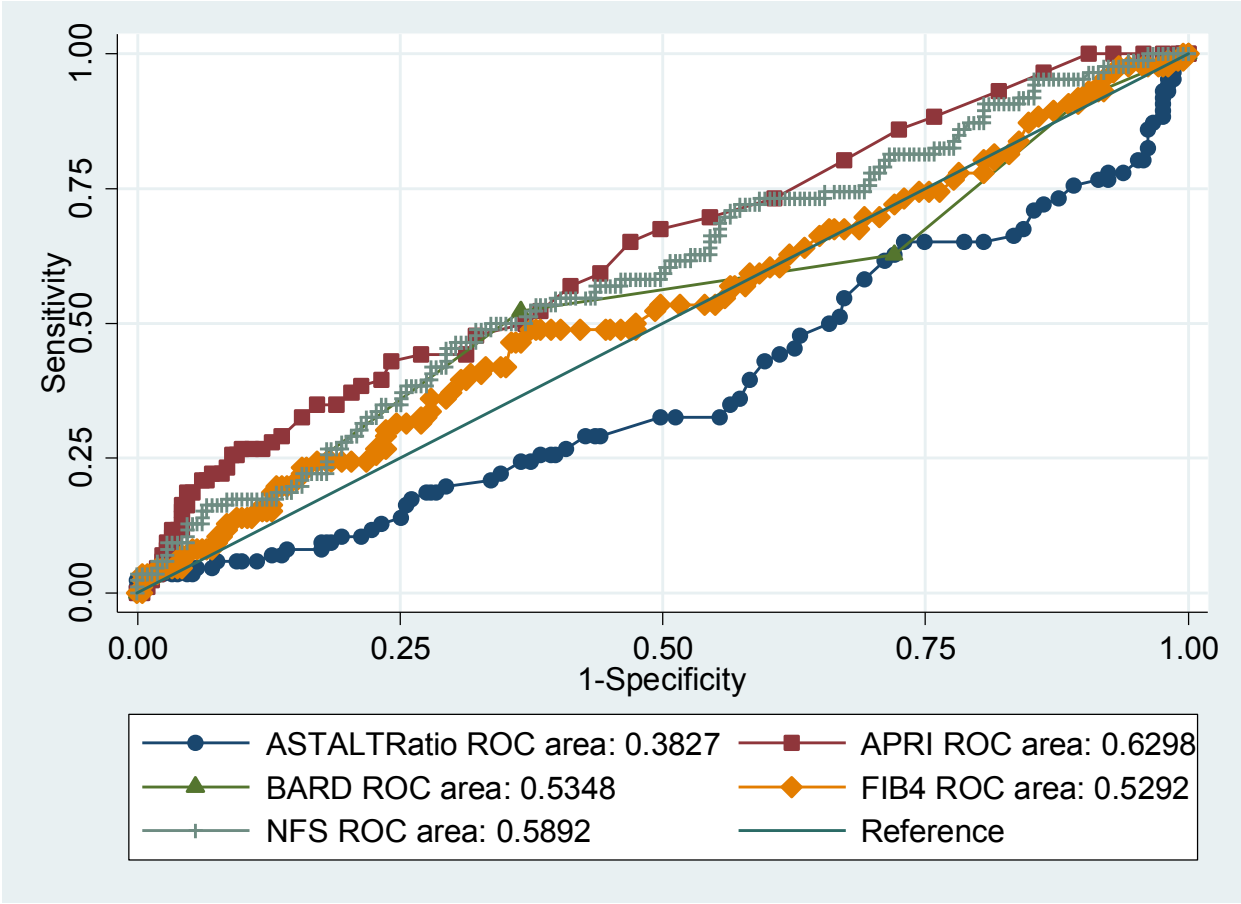


Table 21. Diagnostic Performance of Validated Cutoffs of Serum Fibrosis in the Prediction of Elevated Liver Stiffness Due to Non-Alcoholic Fatty Liver Disease (n=309)								
Variable	**Cut-off**	**AUROC (95%CI)**	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**DOR**	**Accuracy**
AST:ALT Ratio	0.8	0.380 (0.309-0.452)	63.6%	26.2%	25.6%	64.4%	0.623	36.9%
AST:ALT Ratio	1	0.380 (0.309-0.452)	31.8%	50.2%	20.3%	64.9%	0.471	45.0%
APRI	0.5	0.635 (0.566-0.704)	21.8%	93.9%	59.4%	74.5%	4.28	72.9%
APRI	1	0.635 (0.566-0.704)	3.5%	98.6%	50.0%	71.3%	2.49	70.9%
APRI	1.5	0.635 (0.566-0.704)	0%	99.5%	0%	70.8%	0	70.6%
FIB4	1.3	0.531 (0.457-0.605)	40.2%	68.4%	34.3%	73.6%	1.46	60.2%
FIB4	2.67	0.531 (0.457-0.605)	4.6%	98.1%	50.0%	71.5%	2.51	70.9%
BARD Score	2	0.540 (0.466-0.614)	92.0%	9.6%	28.7%	75.0%	1.21	32.9%
NAFLD Fibrosis Score	-1.455	0.590 (0.517-0.662)	82.6%	23.7%	30.6%	76.9%	1.47	40.7%
NAFLD Fibrosis Score	0.676	0.590 (0.517-0.662)	24.4%	82.0%	35.6%	72.7%	1.47	65.3%

ALT = alanine aminotransferase, AST = aspartate aminotransferase, BMI = body mass index

Reducing need for TE scans

Diagnostic thresholds for laboratory tests and body mass index which would have 100% and 90% sensitivity for elevated liver stiffness in NAFLD risk were derived (see table 22). Subsequently, the number of TE scans which would be avoided at these thresholds is shown.

Table 22. Utilisation of Transient Elastography At High Sensitivity Cutoffs of Index Tests for the Prediction of Clinically Significant Non-Alcoholic Fatty Liver Disease (n=309)

Variable	100% Sensitive Cut-off	Transient Elastography Saved (%)	90% Sensitive Cut-off	Transient Elastography Saved (%)
BMI (kg/m^2)	24.0	31 (10.1%)	27.4	90 (29.3%)
Platelet Count (10^9/L)	476	2 (0.7%)	330	46 (15.4%)
ALT (U/L)	4	0 (0%)	16	63 (20.4%)
AST (U/L)	15	18 (5.8%)	17	44 (14.2%)
Bilirubin (µmol/L)	4	3 (1.0%)	5	17 (5.5%)
Albumin (g/L)	48	0 (0%)	43	14 (4.5%)
AST:ALT Ratio	0.41	2 (6.5%)	0.57	13 (4.2%)
APRI	0.15	20 (6.7%)	0.17	45 (15.1%)
FIB4	0.39	1 (0.3%)	0.66	32 (10.7%)
BARD Score	1	0 (0%)	2	28 (9.1%)
NAFLD Fibrosis Score	-2.875	8 (2.7%)	-1.704	49 (16.5%)

As for ALD risk, at cutoffs which were 100% sensitive for predicting elevated liver stiffness, only a significant minority of TE scans would be avoided, 10.1% of TE scans could have been avoided at a BMI cutoff of 24.0. At 90% sensitivity, a number of tests would have avoided more than 10% of scans, and both ALT and BMI cutoffs would have avoided more than 20% of TE scans (20.4% for ALT level of 16U/l and 29.3% for BMI of 27.4kg/m^2 respectively). Body mass index had an AUROC of 0.726 (95% CI 0.666-0.787) for the prediction of elevated liver stiffness. The body mass index cutoff of 27.4 had 90.8% sensitivity, 37.3% specificity, 36.4% positive predictive value and 91.1% negative predictive value for predicting elevated liver stiffness.

Discussion

Key Findings

Following screening of 919 patients with hazardous alcohol use, type 2 diabetes or raised ALT levels, using Transient Elastography and subsequent confirmative investigations, a significant number of previously undiagnosed cirrhosis cases were identified. The total number of cirrhosis cases more than doubled from 23 to 50 cases. The updated estimate of diagnosed cirrhosis prevalence post-study (239.6 cases per 100,000 population) is more than three times UK cirrhosis prevalence estimates from the GPRD of 76.3 cases per 100,000 population(20). Importantly, more than half of patients eligible for screening did not attend; it is therefore likely that yet more undetected cirrhosis cases are present in this primary care population.

Type 2 diabetes and obesity were important risk factors for the diagnosis of cirrhosis; 59% of new cases were attributed to NAFLD alone and a further 30% cases had excessive alcohol intake in addition to diabetes and/or obesity as risk factors for cirrhosis. Furthermore, liver disease prevalence in participants with type 2 diabetes was high. In those patients with type 2 diabetes, elevated liver stiffness (indicative of clinically significant fibrosis) was present in 32% of those with valid liver stiffness measurement, and minimum cirrhosis prevalence in the entire studied primary care type 2 diabetes population is 2%.

Overall, obesity was significantly associated with an increased diagnosis of elevated liver stiffness and cirrhosis. This finding was present in both patients with hazardous alcohol use and type 2 diabetes. Strikingly, compared to non-obese patients, obese patients with hazardous alcohol use were 5.6 times more likely to be diagnosed with cirrhosis and obese patients with type 2 diabetes were 9.4 times more likely to be diagnosed with cirrhosis. Interestingly, despite the significant association of obesity with the diagnosis of elevated liver stiffness and cirrhosis, the prevalence of elevated liver stiffness did not differ between Rushcliffe and Inner City practices (26.8% and 24.8%). This was despite an increased percentage of obese patients in the Inner City practices of 24.3% compared to 12.6% in Rushcliffe practices. Given similar alcohol consumption levels and metabolic syndrome percentage seen in studied patients from the two practice locations the cause for this isn't clear; although a greater percentage of males undergoing

TE in Rushcliffe (67.5% vs. 64.9% in Inner City practices) or older median patient age (64.0 years vs. 58.5 years) might be possible contributors.

In the Inner City subgroup in which the diagnostic performance of alternative measures compared to TE could be assesses, body mass index readings could be used to avoid a significant number of TE scans. With a sensitivity of more than 90% for elevated liver stiffness, a BMI reading of 25.0 would have avoided 38% of scans in patients with ALD risk and a BMI reading of 27.3 would have avoided 29% of scans in patients with NAFLD risk. At these diagnostic cutoffs, the negative predictive value of BMI for predicting elevated liver stiffness was 95% and 91% respectively; far greater than validated thresholds of simple fibrosis markers which performed poorly in this primary care cohort.

Strengths and Limitations

The current study was performed in a large adult primary care population of more than 20,000 adults, of whom more than 10% had hazardous alcohol use and/or type 2 diabetes as risk factors for chronic liver disease. Extending the study to further general practice locations in Inner City Nottingham improved the generalisability of the study population. Moreover, introducing a single reference standard (investigating using TE alone), allowed analysis of simple fibrosis marker performance in primary care and exploration of alternative tests which might avoid the need for TE in some cases.

Overall, 919 patients were investigated with Transient Elastography which represents one of the largest reported studies of liver disease

stratification in a primary care setting. These patients were recruited from geographically distinct areas of Nottingham (from both suburban and inner city primary care practices). The type 2 diabetes prevalence of 4.8% in the studied population is very similar to recent UK estimates(227). The obesity prevalence of 18.3% is slightly lower than the current UK obesity prevalence, albeit an additional 11% of patients in the studied practices did not have a BMI reading recorded. Our results are therefore likely to be generalizable to other regions of the United Kingdom, where using a risk factor based approach to liver disease investigation rather than liver function tests is likely to significantly increase the diagnosis of fibrosis and cirrhosis.

The diagnostic subgroup analysis subsequently performed in the patients attending the Inner City practices occurred in a large diagnostic cohort of more than 500 patients (309 with NAFLD risk and 223 with ALD risk). There was a near complete dataset available for the studied laboratory and simple fibrosis marker tests which were analysed, and a satisfactory number of outcome measures occurred in the studied population (elevated liver stiffness in 20% of ALD risk patients and 29% of NAFLD risk patients). This means the performance of the studied markers is unlikely to be inflated from artificially high negative predictive values due to low study outcome numbers. Unfortunately, due to the additional diagnostic step utilised in the Rushcliffe population and therefore potential selection bias, there is not yet a validation population against which to test the conclusions of body mass index cutoff for avoiding TE. Further study is required in order to show that

these cutoffs retain their diagnostic value in other primary care populations without missing significant amounts of liver disease.

A further strength is use of additional tests to confirm cirrhosis diagnoses, to ensure that cirrhosis diagnoses were not overestimated in the studied population. Although recent guidance has suggested that a liver stiffness reading of greater than 15kPa is strongly suggestive of compensated cirrhosis(209), the positive predictive value of liver stiffness readings in the community may be lower than previous secondary care studies due to reduced disease prevalence. Therefore, rather than use TE results alone, cirrhosis was confirmed with additional supportive radiological, histological and endoscopic evidence, cirrhosis diagnoses reported are therefore robust.

The cirrhosis diagnoses detected in the current study should be regarded as a bare minimum as study uptake was modest, with only 45% of the eligible population undergoing the TE examination. This is, however, superior to the other major UK primary care liver stratification study thus far reported, which enrolled only 35% of patients defined at risk from their alcohol consumption(228). As would be expected with a non-randomised screening study, there was a selection bias with screening attenders being older, less likely to be male and with a differing proportion of hazardous alcohol use and type 2 diabetes than non-attenders which may mean that the non-attenders would be at lower risk of having cirrhosis had they been screened. Whilst I assume the true cirrhosis prevalence is greater than the reported estimates, it is difficult to predict the incremental increase of

cirrhosis which would be diagnosed with 100% screening attendance in view of these differences.

A further limitation is that obesity in the absence of type 2 diabetes was not specifically examined as a risk factor for liver disease in this study. Although by studying patients with type 2 diabetes and raised ALT is likely to have enriched our population with those obese patients most likely to have cirrhosis, it is probable that there are still undetected patients with cirrhosis who have obesity as a lone risk factor or in association with other features of the metabolic syndrome. An estimate of cirrhosis prevalence due to all metabolic risk factors in this primary care cohort cannot therefore be reported. Future studies should examine the prevalence of significant liver disease in otherwise unselected obese patients in order to ascertain whether screening of this group is warranted. There is also evidence from a previous study of assumed healthy individuals that hepatic steatosis, obesity and metabolic syndrome are associated with minor but statistically significant elevations of liver stiffness measurement(229, 230). It is therefore possible that the prevalence of elevated liver stiffness reported in obese subjects overestimates the presence of liver fibrosis. However, for cirrhosis diagnosis, further corroborative evidence was utilised. I am therefore confident that NAFLD cirrhosis diagnoses and the impact of obesity with regards to cirrhosis diagnosis in the study population are accurate.

There are also specific limitations to discuss from the diagnostic analyses performed in the Inner City patients. TE and liver stiffness measurement might be considered an imperfect gold standard as it doesn't

predict the staging of fibrosis on liver biopsy with 100% accuracy. An elevated liver stiffness (≥8 kilopascals) was chosen as a pragmatic gold standard for a number of reasons. Firstly, liver biopsy is an invasive and specialist test – it isn't possible to perform liver biopsy on all participants in a primary care screening study. Secondly, both prior study(155) and the histology data displayed in chapter 3 show this liver stiffness cutoff to be highly predictive of the presence of liver fibrosis. Thirdly, in the current study elevated liver stiffness resulted in a change in management (hepatologist review and consideration of further investigations). Therefore, in this population, elevated liver stiffness is a reasonable test to use as a reference standard against which to measure the diagnostic performance of simple fibrosis markers. In the current study, these tests (APRI, AST:ALT ratio, BARD score, FIB4 and NAFLD fibrosis score) were poor predictors of elevated liver stiffness, and would have only avoided the need for TE accurately in a small number of cases. This is possibly because these simple fibrosis markers were derived to optimise their negative predictive value for excluding advanced liver fibrosis rather than to exclude all cases of liver fibrosis (which a liver stiffness measurement of 8 kilopascals is likely to represent in primary care). Further study in larger primary care populations, where there are enough cases of advanced fibrosis or cirrhosis to be the outcome measure for analysing simple fibrosis marker diagnostic performance, should therefore be considered.

Comparison with other studies

The current study highlights the significant impact of obesity in determining those patients with hazardous alcohol use who were diagnosed

with elevated liver stiffness or cirrhosis. As body mass index increases, the percentage of patients at risk from NAFLD also rises. For example, in a metaanalysis of 1,600 patients undergoing bariatric surgery and paired liver biopsy, 91% patients had NAFLD, 37% had non-alcoholic steatohepatitis, 60% had hepatic fibrosis and 1.7% were cirrhotic(63).

Subsequently, two large epidemiological studies from the UK have demonstrated the important synergism between body mass index and alcohol in predicting cirrhosis development and liver-related mortality. The first was an analysis of 1.3 million women who were studied as part of breast cancer screening in the Million Women Study(34). A significantly increased risk of cirrhosis development during a median 6 years of follow up was observed in participants who consumed between 70 and 150 grams per week alcohol consumption at normal weight (HR 1.59; 95% CI 1.31-1.92), a risk which rose further in overweight (HR 1.83; 95% CI 1.56-2.16) and obese participants (HR 2.31, 95% CI 1.83-2.94). The second study 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 BMI (overweight or obese patients) was not significantly different from baseline (HR 1.29, 95% CI 0.60-2.80), and far less than risk attributable to alcohol (consumption ≥15 units per week) (HR 3.66, 95% CI 1.74-7.71), the interaction of both BMI and alcohol greatly exceeded the risk from either factor alone or the expected product of the two (HR 9.53, 95% CI 4.98-18.2)(33).

A 2.0% minimum prevalence of cirrhosis in patients with type 2 diabetes was observed which is in keeping with previous studies which have

used TE in hospital based cohorts of type 2 diabetes. An Australian study investigated 81 patients with type 2 diabetes from their secondary care clinics using TE followed by liver biopsy in accepting patients(231). Using a similar cutoff for elevated liver stiffness to the present study (7.65 kilopascals), abnormal TE was observed in 35% of patients with valid scans, and cirrhosis prevalence of 2.5% following confirmatory liver biopsy. A larger French study by Jacqueminet et al investigated 1,131 patients with type 2 diabetes in France using Fibrotest (a complex serum biomarker panel) followed by reinvestigation with TE. Advanced fibrosis prevalence was 2.8% in this cohort and cirrhosis prevalence was 0.7%(232). Although this is a lower prevalence than in the present study, in Jacqueminet's study 21 cirrhotic patients were excluded a priori; when considering these patients in addition their type 2 diabetes cirrhosis prevalence rises to 2.4%. Similarly, in a cohort of 141 participants with type 2 diabetes and 60 healthy controls who were investigated with ultrasound and TE, Sobhonslidsuk et al demonstrated an advanced fibrosis prevalence (defined as liver stiffness >7kPa) of 16.1% in the type 2 diabetes group compared to only 1.7% in the control group(233). Lastly, in a recently published study of 3,041 individuals aged over 45 years from Rotterdam, 5.6% had liver stiffness≥8kPa, but this rose to 17.2% in individuals with diabetes and steatosis(234).

The only other primary care-based study of liver stiffness in patients with type 2 diabetes used magnetic resonance elastography rather than TE. In this study, Doycheva et al investigated 98 patients and showed an advanced fibrosis of 7.1%(235). Of NAFLD patients identified, only 26% had

elevated ALT levels, again highlighting that the majority of patients with type 2 diabetes and chronic liver disease would be missed by investigating with liver function tests alone.

Although the current study showed that body mass index measurement outperformed simple fibrosis markers for the prediction of elevated liver stiffness, few studies have investigated body mass index alone as a predictive biomarker for liver fibrosis. BMI is however part of the panel of variables which make up the BARD and NAFLD fibrosis scores, and was one of the independent predictors of advanced fibrosis in the derivation studies for these tests(212, 213). These simple fibrosis markers (in addition to AST:ALT ratio, APRI and FIB4) had poor diagnostic performance for predicting elevated liver stiffness in both patients with ALD risk and NAFLD risk.

This is the first time that analysis of these markers in patients at risk of ALD in a primary care population has been reported, although several secondary care studies have also shown these tests to be inadequate predictors of liver fibrosis and inferior to TE(164, 171, 172, 223). However, in secondary care populations with NAFLD, a large number of studies have shown high negative predictive values (>90%) for advanced liver fibrosis(181-183, 212-215, 219). There were therefore grounds for optimism that this would remain the case in primary care, but the diagnostic performance in the current study was poor. In addition to the impact of elevated liver stiffness as the reference standard investigation as explained above, this may be explained by the target condition differing from these

previous secondary care studies. Rather than a cohort of patients with known NAFLD, in the current study patients with type 2 diabetes were screened of whom approximately two thirds would have been expected to have NAFLD(68). Furthermore, our study participants were screened even if liver function tests were normal, whilst patients in the aforementioned secondary care studies would have been pre-selected due to abnormality of liver enzymes or other high risk clinical features.

Overall, it appears that these simple fibrosis markers do not have a role in reducing the number of TE scans required in primary care screening of patients with type 2 diabetes. Whether this remains the case if patients were screened on the basis of obesity alone requires additional study.

Implications

This study highlights the fact that multiple risk factors for chronic liver disease exist in a community setting. Specifically, 44% of our population undergoing transient elastography had two or more risk factors of hazardous alcohol use, type 2 diabetes or obesity. The current study demonstrates the important synergism of alcohol consumption and metabolic risk factors in determining which patients had prevalent liver disease. 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%. In comparison, patients with hazardous alcohol use alone had a much lower cirrhosis prevalence of 1.4%, and elevated liver stiffness in only 14.5%. The concept of strictly dichotomising patients with ALD and NAFLD risk factors on the basis of a specific cut-off of alcohol consumption does not take into

account the interactions and synergisms between these risk factors in the population. Therefore definitions of ALD and NAFLD as clinical entities need updating, particularly to clarify that NAFLD should not be discounted in the presence of hazardous alcohol use and ensure clinical practice and public health policy tackles both hazardous alcohol use and metabolic risk factors in synchrony.

The current study further highlights the important prevalence of clinically significant liver disease, particularly in those patients with type 2 diabetes. Given the high prevalence of both elevated liver stiffness and cirrhosis detected in patients with type 2 diabetes, and proof of concept now established in several studies, future studies should focus on the unanswered questions from Wilson and Jungner/National Screening Criteria to consider formal screening for liver disease using TE in primary care as on a national scale. For example, future studies should screen a larger population of patients with type 2 diabetes (for example, at a clinical commissioning group or district level) to ensure that TE remains a feasible tool to stratify these patients. Such screening programmes, in addition to facilitating uptake of lifestyle measures, will allow optimal medication management of these individuals with antidiabetic medication which will also treat NASH, such as pioglitazone(236) or liraglutide(237). In addition, both the cost effectiveness and upfront cost to healthcare are important further considerations, as is the development of agreed policy for continued case finding e.g. the interval of repeat TE scans in those patients with initially normal liver stiffness results.

An alternative option is for selective screening and surveillance based on the type and number of risk factors. In this study the high risk strata includes alcohol/obesity, diabetes/obesity, alcohol/diabetes and alcohol/diabetes/obesity. The minimum prevalence of cirrhosis ranged from 2.9% to 13.3% in these groups. Further refinement of which risk factors contribute to the greatest yield of significant liver disease is required. In addition, specific body mass index thresholds to optimise investigation of high risk patients (≥25.0 in patients with hazardous alcohol use and ≥27.3 in those with metabolic risk factors) require validation in an independent primary care population before incorporation into clinical practice. This will allow focussed screening with appropriate diagnostic tools, proportionate therapeutic intervention and tailored follow up of patients with chronic liver disease in the community.

Summary

Using Transient Elastography to screen for liver disease primary care resulted in significantly increased diagnosis of cirrhosis. The diagnosed cirrhosis prevalence following the study was more than double the estimate in this population pre-study, and more than 3 times greater than previous GPRD UK population estimates. The majority of newly identified cirrhosis cases had type 2 diabetes or obesity as risk factors (and therefore, presumably had NAFLD) or had alcohol excess as an additional risk factor. The combination of hazardous alcohol use, obesity and type 2 diabetes had a significant impact on the percentage of diagnoses of elevated liver stiffness and cirrhosis. Focussing upon the combination of liver disease risk factors is

likely to be the most effective way of designing cost effective investigation pathways, and relevant interventions, for patients in the general population.

Chapter 5: Patients' Experiences of Investigation for Chronic Liver Disease in Primary Care: A Qualitative Study

Introduction

As outlined in chapter 1, the rising incidence of cirrhosis and associated increase in liver-related mortality are driven by both increasing lifestyle-related risk factors for hepatic fibrosis (hazardous alcohol use and type 2 diabetes in particular), and inadequate traditional approaches to liver disease identification. Chapters 3 and 4 have demonstrated that focussing investigations instead on these risk factors, and screening these patients in a community setting with Transient Elastography (TE) significantly increases the identification of both clinically significant liver disease and liver cirrhosis.

Early detection of asymptomatic liver disease provides an opportunity for targeted lifestyle interventions which are likely to improve long term prognosis(204). For ALD and NAFLD, lifestyle alterations of alcohol moderation and weight loss through a combination of dietary improvement and increased physical activity respectively form the mainstays of treatment.

However, despite the significant potential health benefits, changes to lifestyle-related behaviour are poorly adopted by patients. For example, numbers needed to treat for brief interventions of alcohol to achieve significant reductions in alcohol consumption are 8-10 (132). Subsequent one year relapse rates of as high as 67-81% have been shown in secondary care studies(28). Ongoing sedentary lifestyle is common in patients with NAFLD risk factors. A questionnaire study of 406 patients attending clinic with diabetes (of whom 81% were type 2 diabetics) showed that less than a

third had undertaken any episodes of moderate or greater exercise in the previous two weeks(238), with numerous barriers to lifestyle intervention identified including perceived difficulty in taking part in exercise, fatigue, lack of time and distractions at home. Even in research trials with a motivated patient population, only the minority of patients achieve weight reduction targets which are associated with significant improvements in liver histology – less than half of participants achieve a 7% weight loss target(92), and as few as 15% of patients achieve a target of 10% weight reduction(239). Novel approaches are therefore required to increase the adoption of behavioural change at a general population level and avert the rising trend of incident cirrhosis and premature death.

Previous studies have demonstrated that feedback of diagnostic information using novel numerical biomarkers may achieve more than a doubling of smoking cessation rates compared to more standard results feedback (240, 241). It is likely this is achieved by demonstrating to patients in an understandable manner that they may have already caused themselves physical harm through an unhealthy lifestyle, and subsequently increasing their motivation for health behaviour change (242). As described earlier in this thesis, the TE device provides an immediate numerical value for liver stiffness, allowing feedback to patients of their risk of significant liver disease during the same investigation appointment. Although results for liver stiffness are on a wide numerical scale, these can be dichotomised to simply demonstrate physical harm to patients (a liver threshold of 8 kilopascals provides accurate identification of liver scarring (155), and therefore

increased risk of progressive liver disease). Similar to the aforementioned smoking cessation biomarkers, it is possible that TE measurement, in addition to accurate cross-sectional liver disease information, provides a 'therapeutic' element by acting as a useful adjunct to patients adopting beneficial health-related lifestyle changes.

The adoption of lifestyle change in patients diagnosed with chronic liver disease has to date had limited study. There are no studies formally assessing the potential behavioural impact of liver disease screening with TE. The use of qualitative research techniques is ideal to develop preliminary information about patient experience, attitudes and values of these currently ill-defined areas, which cannot be necessarily covered in adequate depth by quantitative or questionnaire studies (243). There are few qualitative studies describing the patient experience of chronic liver disease, with previous literature focussing upon more uncommon diagnoses such as primary biliary cirrhosis and liver transplantation(244).

An in-depth description of patient experience of more common lifestyle related liver disease, and the facilitators and barriers to adopting lifestyle interventions could be crucial to aid design of relevant patient-centred diagnostic and behavioural interventions, which are well adhered to and have a significant impact on future cirrhosis incidence and mortality. Related to this, there is also the need to build upon the findings of the few previous qualitative studies exploring liver disease screening in primary care, including the acceptability of screening in the general population and the potential behaviour effects of both positive and negative liver biomarker results(245, 246).

The overall objective of this interview study was to provide preliminary data on the patient experience of liver disease screening using TE, and related facilitators and barriers to adoption of recommended lifestyle changes. In particular, the aims were:

1/ To map the experiences of patients undergoing TE in a community setting for identifying clinically significant chronic liver disease

2/ To establish whether investigation of patients at-risk of chronic liver disease in primary care alters pre-existing health beliefs

3/ To explore the factors associated with patients' adherence to, or avoidance of, sustained lifestyle change to tackle risk factors associated with chronic liver disease.

Methods

The Nottingham Community Liver Study

The methodology for recruitment of patients to the Nottingham Community Liver Study has been described in detail in chapters 3 and 4. In summary, patients with defined risk factors for development of chronic liver disease (hazardous alcohol intake, type 2 diabetes, and/or persistently raised ALT liver enzyme without known cause) were invited to attend a liver scan appointment at their primary care practice. Transient Elastography (Fibroscan), a portable scanning device based upon ultrasound which measures liver stiffness(184), was performed by trained hospital nurses. At the TE scan appointment, participants were asked to provide consent to be approached for a semi-structured interview at a later date as part of a longitudinal cohort study (see Appendix H; written consent was obtained

in >90% of patients). Detailed information on the demographic and clinical characteristics of the study populations are provided previously in chapters 3 and 4).

Study Design and Participants

Patients who underwent stratification of chronic liver disease in the community using Transient Elastography as part of either phase of the Nottingham Community Liver Study were eligible for this qualitative study. Participation in interviews was voluntary, and all patients provided informed written consent.

Participants were purposively sampled aiming for a representative sample of those undergoing chronic liver disease stratification within the community. A priori sampling strata were selected based upon fundamental differences in screening experience which were likely to impact upon the participant description of studied phenomena(247). Sampling strata were i) GP surgery location (suburban (Rushcliffe) versus Inner City Nottingham), ii) liver disease risk factor (hazardous alcohol use vs. type 2 diabetes), and iii) diagnosis assigned after community liver disease stratification (normal liver stiffness vs. liver fibrosis vs. cirrhosis).

To facilitate discussion of the short and medium term sustainability of lifestyle changes, participants were only interviewed at least 6 months after undergoing the Transient Elastography scan. Participants who had undergone TE more than 2 years prior to interview commencement were excluded as a previous qualitative study demonstrated that patient description of liver biomarker information after this time interval is

significantly limited by recall bias(246). Patients were also excluded if they were unwilling to provide consent for interview, or if they were unable to communicate in English.

Interview Schedule

One-to-one semi-structured interviews were conducted by a single researcher (DH). As highlighted by Ritchie et al(247)(p. 47-70), one-to-one interviews "provide deep focus on the individual, an opportunity for detailed investigation of each person's individual perspective, for in-depth understanding of the personal context within which the research phenomenon is located, and for very detailed subject coverage". Semi-structured interviews were utilised as they enable exploration of pre-defined objectives by researchers, whilst offering the flexibility to address issues uncovered by the participants which had not been considered by the research team (248).

A preliminary semi-structured interview guide was derived (by DH) prior to study commencement. The interview guide (Appendix J) explored participant experience of liver disease screening in the community, facilitators and barriers to the adoption of lifestyle changes following the liver scan, and the sustainability of such lifestyle change, where relevant. The utilisation of predominantly open-ended questions allowed the researcher to diverge and pursue avenues of interest when these arose (248-250). Probes were used where necessary to amplify or expand upon interesting responses from participants(247)(p.177-208), whilst leading questions which would impact upon the validity of participant's responses were avoided. The

interview guide was reviewed by the researcher's qualitative supervisor (MB) who was independent to the Nottingham Community Liver Study investigations, to ensure that the questions would elicit a rich and complex account of the phenomena under study. The interview guide was piloted with one research nurse (independent to the Nottingham Community Liver Study; data not shown) and during the initial 3 participant interviews to ensure that relevant and reliable interview data were captured(243). As only minor iterations to the interview guide occurred during this process, data from the initial patient interviews were included in the final sample for analysis (Table 23; participants 1-3).

Interview Procedure

Participants were invited to take part in a face-to-face interview; appointments were arranged via telephone from the pool of eligible patients who provided consent allowing approach for interview following their liver scan appointment. Interviews took place either in the patient's home or an interview room at the Nottingham Digestive Diseases Biomedical Research Unit. The location was chosen according to patient preference, to ensure they were relaxed within the interview environment and therefore comfortable to provide their interview responses(251).

Participants were provided with a patient information sheet (Appendix I), which outlined the interview procedure and aims of the study. They were given an opportunity to ask any questions regarding the interview procedure and/or study before providing written informed consent (Appendix H) prior to commencement of the interview. Participants were aware that their interview

data would be treated confidentially, and that they were free to withdraw at any time. The researcher's supervisor observed the first two patient interviews to ensure credible interview practice and correct utilisation of the interview guide by the researcher. The eighteen subsequent interviews were conducted by the researcher alone. Interviews continued until data saturation were reached, which was when additional interviews failed to provide new themes or insights to the phenomena being studied(252), whilst ensuring adequate representation of each pre-defined sampling stratum.

In total, twenty interviews were conducted (mean interview length 27.6 minutes; standard deviation 7.6; range 16-46 minutes). All interviews were digitally audio-recorded and transcribed verbatim by an external specialist transcription company.

Analysis

Once received, interview transcripts were checked to ensure all personal identifiers had been removed. Interview transcripts were read in full whilst concurrently listening to the digital interview file, to enable correction of any errors made during the transcription process.

Interview data were analysed thematically, using an inductive approach as advocated by Braun and Clarke(253). Thematic analysis is a widely used method for "identifying, analysing and reporting patterns (themes) within qualitative interview data"(253). Benefits of thematic analysis include its pre-defined structure, which enables accessibility for a novice qualitative researcher (as in the current study) to develop the necessary skills for robust qualitative analysis, whilst allowing the flexibility to adopt numerous

philosophical worldviews(247)(p. 269-295). Moreover, this structure allows generation of an 'auditable trail' of data analysed, ensuring transparency of the analytical processes employed and so enabling readers to be able to critically appraise the study findings (249, 254).

Briefly, the stages of thematic analysis utilised during the current study were:

i) **Familiarisation with the dataset** – systematic 'active' reading of each interview transcript was undertaken on several occasions, in order to familiarise the researcher with the interview content. Preliminary ideas for codes were noted during this stage of the process.

ii) **Generation of initial codes** – data extracts were assigned codes which identified a feature which the researcher found interesting. As described by Boyatzis(255), codes are "the most basic segment, or element, of the raw data or information that can be assessed in a meaningful way regarding the phenomenon". Initial codes were descriptive and stayed true to the participant's accounts. To improve the reliability of coding assignment by the researcher, the researcher's supervisor (MB) independently coded the five richest interview transcripts(256). The preliminary coding assignment after coding of all twenty transcripts is provided in Appendix K.

iii) **Searching for themes** – the analysis was then re-focussed at a broader level, with sorting and grouping of the codes and attached data extracts into analytical categories or 'themes'. Themes "capture something important about the data in relation to the

research question"(253) and interpret meaning within the dataset. Importantly, themes were defined on the basis of capturing something important to the research question, rather than purely upon the prevalence of individual or groups of codes. Analysis became more abstract at this stage, with interpretation of the meaning of the data rather than pure description. A 'constant comparative' method was used in which individual data items were compared to the rest of the dataset to ensure preliminary themes retained importance with additional interviews(257). Interview data were analysed from a constructionist viewpoint. As described by Mays (249) "there is no way in which the researcher can in any sense capture the literal truth of events". It is important to acknowledge, therefore, that the research interview is an interaction between the participant and researcher, and that this relationship will shape the interview data generated(247)(p.177-208). Participant responses should not be taken at face value(258, 259), but rather considered as a "window to the participant's social world"(247)(p.269-295). The initial themes and sub-themes derived are provided in Appendix L, and were reviewed with the researcher's supervisor (MB) prior to the next stage of thematic analysis.

iv) **Reviewing themes** – themes were refined to ensure data cohered together meaningfully, whilst themes were clear and distinct(253). This required review of the validity of individual data extracts within

themes, and validity of individual themes to the entire dataset, with subsequent reorganisation and collapsing of themes as required.

v) **Defining and naming themes** – for each theme a detailed analysis was conducted and written, identifying the 'story' that each theme tells both within itself and related to the entire dataset.

Following agreement of the coding structure and preliminary themes between the researcher and supervisor, NVivo 11 (QSR International Ltd, Melbourne, Australia) was used as a data management tool. Core themes, and important subthemes, are reported in the results section, with selection of data extracts which provide "sufficient evidence of the themes within the data"(253).

Reflexivity Statement

It is important that the researcher reflects on the ways in which they may have impacted upon participant responses(260). For the current study, it is important to acknowledge that I co-designed and led the Nottingham Community Liver Study, and as part of the study design had previously met the participants with elevated liver stiffness (n=13) at a single hepatology clinic visit. As a lone qualitative researcher it would likely have introduced an element of bias in terms of interview guide development, participant interview responses and thematic analysis. However, the researcher's supervisor (MB) was independent to the Nottingham Community Liver Study conduct, and her expertise was utilised to improve the validity of the current study. Her input with derivation of the interview guide, observation of early interviews, and in

particular secondary analysis of rich transcripts were all validation measures taken to limit these pre-existing biases.

Ethical Approval

Ethical approval for this qualitative study was sought as part of the main ethical application for the Nottingham Community Liver Study, and approved by the East Midlands – Leicester Research Ethics Committee (13/EM/0123). Subsequently, a substantial amendment was approved on 10th June 2014, which included the participant consent form signed by patients immediately prior to interview (Appendix H) and preliminary interview schedule (Appendix J).

Results

Participants

In total 28 participants were invited for interview between July 2014 and December 2014; 8 declined to take part whilst the remaining 20 participants completed the interview. Summary characteristics for the 20 patients who completed the interview are provided in Table 23. Mean participant age was 57.9 years (standard deviation = 9.3; range 40-71 years), and 12 participants (60%) were male. Both of these demographic features are representative of the entire study population undergoing liver scan. Participants were adequately distributed within the sampling strata; 8 (40%) participants were from suburban GP practices versus 12 (60%) from Inner City Practices, 8 (40%) participants with hazardous alcohol use versus 12 (60%) with type 2 diabetes as their chronic liver disease risk factor, and 7 (35%) patients with normal liver stiffness, 7 (35%) with liver fibrosis and 6

(30%) with cirrhosis respectively. The majority of interviews (14 participants) were performed in the participant's home, whilst the other 6 interviews took place at the NDDC BRU.

Table 23. Demographic and Clinical Characteristics of Interviewed Patients (n=20)

Participant	Age	Gender	GP Location	Liver Risk Factor	TE Result*
1	48	Female	Inner City	Alcohol	Abnormal - Cirrhosis
2	65	Female	Inner City	Type 2 Diabetes	Abnormal - Cirrhosis
3	66	Female	Suburban	Type 2 Diabetes	Abnormal - Fibrosis
4	71	Female	Suburban	Type 2 Diabetes	Abnormal - Fibrosis
5	66	Male	Suburban	Type 2 Diabetes	Normal
6	55	Female	Suburban	Type 2 Diabetes	Abnormal - Cirrhosis
7	64	Female	Inner City	Type 2 Diabetes	Abnormal - Cirrhosis
8	61	Male	Suburban	Type 2 Diabetes	Normal
9	69	Male	Inner City	Type 2 Diabetes	Abnormal - Fibrosis
10	62	Male	Suburban	Alcohol	Normal
11	46	Female	Inner City	Alcohol	Abnormal - Fibrosis
12	63	Male	Inner City	Alcohol	Normal
13	46	Male	Inner City	Type 2 Diabetes	Abnormal - Fibrosis
14	67	Male	Inner City	Alcohol	Abnormal - Cirrhosis
15	45	Female	Inner City	Alcohol	Normal
16	45	Male	Inner City	Type 2 Diabetes	Abnormal - Fibrosis
17	40	Male	Suburban	Type 2 Diabetes	Normal
18	61	Male	Inner City	Alcohol	Abnormal - Fibrosis
19	63	Male	Suburban	Type 2 Diabetes	Abnormal - Cirrhosis
20	54	Male	Inner City	Alcohol	Normal

*TE result refers to diagnosis assigned on the basis of Transient Elastography (Fibroscan) reading of liver stiffness, and subsequent confirmatory tests for abnormal scan to determine whether cirrhosis was present.

Themes

Five themes, with a total of 9 corresponding sub-themes were identified during the thematic analysis process – these are listed in table 24. Key themes are presented in order of chronology through the patient experience of community liver disease screening; these are discussed in turn with extracts from interviews to reflect the overall views of participants.

Table 24. Key themes and sub-themes identified from thematic analysis

Key Themes	Sub-Themes
- Patient knowledge and health perception pre-screening	- *Perceptions of own health and lifestyle* - *Knowledge of lifestyle-related health risk for liver disease*
- Experience of liver disease screening	- *Acceptability and understanding of screening process* - *Participant interpretation of numerical liver stiffness result*
- Initial impact of liver stiffness result	- *Generating shock or anxiety* - *Increasing awareness of liver-related health and contemplating lifestyle changes*
- Initiating lifestyle change	- *Role of liver disease screening* - *Facilitators of lifestyle change* - *Barriers to lifestyle change*
- Repeating liver disease screening in the future	

1. Patient knowledge and health perception pre-screening

When considering the impact of liver disease screening on individuals, it is important to evaluate both the participant's pre-existing perception of their health and knowledge of which aspects of their lifestyle might contribute to an increased risk of adverse health. The following two sub-themes describe these phenomena and consider the features which have contributed to shape participants' views of their health.

a) Perceptions of own health and lifestyle

Participants with type 2 diabetes described their experiences of both their diabetes diagnosis, and opinion of their diabetes control prior to their liver scan appointment. Some participants described their experience of significant symptoms such as weight loss, fatigue and excessive thirst, which prompted the investigation and diagnosis of their diabetes that appeared to impact their opinion of future diabetes control. Subsequently there appeared to be two separate views of what defined adequate diabetes control in the patient's view. Firstly, a 'medical' view where participants were aware of GP and specialist nurse targets for defining good glycaemic control and subsequent medication choices.

> *So now I'm on tablets but they are talking, because it's gone out of control, I can't seem to get it back down to the levels that they want, they're talking about giving me non-insulin injections but I shall find out later this month about that.* Participant 6, Type 2 Diabetes, Suburban GP, Liver Cirrhosis

However, a second, more dominant view existed where a lack of current symptoms resulted in patients perceiving that they were healthy, despite poor control of their diabetes according to medical targets.

> *I went back onto some medication, while taking my blood sugar, it went really strange, my lowest reading ever was 2.4 and I was perfectly fine and my highest reading was up to 27 and I was perfectly fine and all the other readings in between, I was perfectly fine, so nobody could figure out what was going on…… But I don't feel any different, doesn't matter what blood sugar levels are, I don't feel any different.* Participant 16, Type 2 Diabetes, Inner City GP, Liver Fibrosis

> *As they say, at the end of the day it will get worse over time anyway but it had reached a point where they were looking at insulin. Oddly at the time, I was feeling better than I had felt in quite some time so I was a bit shocked when she said that to me, but we left it, agreed to leave it six months and for me to take my medication a bit more regularly and properly, seriously and so far, touch wood, it seems to be okay.* Participant 17, Type 2 Diabetes, Suburban GP, Normal liver scan

Several patients with hazardous alcohol use described their experiences of symptoms related to their alcohol excess. These symptoms resulted in significant anxiety, and prompted realisation that their alcohol use was impacting their health adversely; both self-mediated attempts to reduce

or stop alcohol, and seeking help from their GP were reported, subsequently resulting in referral for a TE scan appointment.

So tell me what's happened with your alcohol since then.

Well it's like basically, I went back, I self-referred myself because it's like when I was drinking too much, I was getting into states like blackouts and that was kind of worrying me 'cause I literally don't know or remember what I've done after and so I thought you know…
Participant 15, Hazardous alcohol, Inner City GP, Normal liver scan

Despite the perception of being in good health, many participants (both with type 2 diabetes and hazardous alcohol use) reported significant co-morbidities which impacted their activity. Most commonly discussed co-morbidities were longstanding musculoskeletal issues, although mobility issues due to a stroke (participant 5), COPD (participant 18) and polymyalgia rheumatica (participant 3) were also reported. These co-morbidities were described as significant reasons for a previous inability to lose weight or perform meaningful exercise; although several participants stressed that they remained as active as their co-morbidities allowed.

Does that impact on your daily life, your exercise or activity?

It does a little bit because I have to wear a knee support and ankle support for old injuries I had a long time ago, they're just there but I just get on with it, you can sit down and put your legs up and do nothing and I'll often play golf, so I'm not going to let it interfere with

that. Participant 12, Hazardous alcohol, Inner City GP, Normal liver scan

Most participants with type 2 diabetes had changed their diet following their diabetes diagnosis. This appeared a more attractive option to participants than increased physical activity, due to the presence of co-morbidities which impacted their mobility.

I've tried to lose weight in the past but because of injury or another, without the exercise, you can't do it and I've got degenerative knee condition in both knees, I can only do limited amounts before my knees pack up but if they do, you're talking a month, two months before I'm able to do anything again. Participant 16, Type 2 Diabetes, Inner City GP, Liver Fibrosis

The dietary changes which were made resulted from a combination of both the impact of the new diagnosis itself, but also learning of the importance of dietary change to prevent future complications of diabetes from the GP team and local diabetes education courses.

Well I was speaking to the diabetic nurse and said I'd like to increase it but it's the cost, she said "I can put you on this programme", so that's when I went onto that, it's quite good. About an hour and a half odd of hard graft, they recommend diet and all this, that and the other, it's been good. Participant 9, Type 2 diabetes, Inner City GP, liver fibrosis

Participants reported that previous medical advice and education courses related to type 2 diabetes primarily focused upon dietary interventions. There was far less mention during the interviews of advice regarding physical activity or exercise.

> ***And what kind of things were you doing when you were trying to lose the weight before the scan?***
>
> *Just cutting down on portion sizes and I'd been to see my local chemist were doing a special, not a diet but just where you could go and talk to them and I started doing that with them and I went in every week, got weighed and it was just somebody to encourage you and I went on a healthy eating course, arranged through, I forgot what it's called now but it's another scheme from the National Health and I went on that, that was a six week course of healthy eating and you learned a lot about portion sizes, which I knew I over-ate anyway but that was very interesting, I found that helpful.* Participant 7, Type 2 Diabetes, Inner City GP, Liver Cirrhosis

b) Knowledge of lifestyle-related health risk for liver disease

Before the liver scan appointment, hazardous alcohol use was recognised to be an important cause of liver disease by all bar one of the participants. This pre-existing knowledge was acquired from a number of sources, such as reports in the media or as described by one participant, via workshops held at his place of work.

Before the scan, what were you aware of as far as things that can cause liver problems in people, per se?

Medication, drinking, obesity, that's about it really that I'm aware of.

How have you picked up that knowledge?

Media, TV, every so often they bash this and they bash that and they bash the other and they'll mention the symptoms and what it can do and what it can't do, so really you tend to get it from the media. Participant 20, Hazardous Alcohol, Inner City GP, Normal liver scan

Several participants described how close family or friends had experienced symptoms or death due to cirrhosis, which had a number of subsequent effects on both knowledge and awareness of their own health. One participant (participant 10) described how his mother's harmful alcohol use and subsequent death due to liver failure created an awareness of his own alcohol use, but also facilitated his wish to undergo liver disease screening to determine his own risk.

Did your mother's illness have an impact on wanting to have the scan done at all?

It did in a way, yeah because don't want to be going down that road, so yeah it did in a way. And other people I'd known have suffered from it as well so it, that sort of decided definitely to get it done. Participant 10, Hazardous alcohol, Suburban GP, Normal liver stiffness

As well as knowing that alcohol was a cause of liver disease, some participants also described specific symptoms of liver disease gained from these experiences of friends and family, including yellowing of the skin (jaundice) and bleeding attributed to liver disease.

> ***You said you knew people with cirrhosis, what was that experience? Who was it and what had they had wrong with them?***
>
> *I used to work with a bloke, he was an alcoholic, plain and simple. He was taken into hospital numerous times because of his liver packing up, he was down to 10ml of liquid in a day at one point, that's how ill he was, where he had to pack up drinking totally or die. So he did…I didn't realise you could be that colour yellow as a person..... It's a bit of a wakeup call if you actually see somebody who drinks that much and you see what happens to them.* Participant 16, Type 2 diabetes, Inner City GP, Liver fibrosis

The term 'alcoholic' was commonly used in participant's descriptions of family and friends who were diagnosed with liver disease. This term appeared to be defined based upon alcohol consumption levels which resulted in a diagnosis of liver disease in this peer group.

> *I just assumed cirrhosis was an alcoholic problem, especially when I've got an uncle that was very close to being alcoholic and having problems.*
>
> ***Did you have personal experience of your uncle with the liver?***

Yes. I class him as an alcoholic, he doesn't class himself as one but I class him as an alcoholic because he can go through a couple of bottles of whisky in a week. Participant 6, Type 2 diabetes, Suburban GP, Liver cirrhosis

Although knowledge of alcohol use and the risk of liver disease were good, most patients considered that alcohol use was the only cause of liver disease. Prior to the liver scan, only one participant (Participant 20) was aware that obesity could lead to liver disease, and strikingly none of the participants were aware that type 2 diabetes was a risk factor for liver disease.

I never thought there would be a problem to be honest. Not being a drinker, you don't think that … sort of thing could happen. I guess I've never really thought much about the liver, probably one of those forgotten, well anything inside is really forgotten, it's in there, you eat as healthy as you can and hope that everything's all right…… because I don't know why, I suppose like most people, I just assumed cirrhosis was an alcoholic problem. Participant 6, Type 2 diabetes, Suburban GP, Liver cirrhosis

Before you had the scan and were aware of the scanning process, were you aware of things that can cause liver problems?

I knew alcohol caused liver problems for definite but I didn't know about diabetes, that came as a surprise when it was mentioned, when

the nurse mentioned it first and then when I saw the consultant.
Participant 19, Type 2 diabetes, Suburban GP, Liver cirrhosis

Although overall knowledge of alcohol use as a risk factor for liver disease was good, awareness of personal risk of liver disease in patients with hazardous alcohol use varied. A couple of participants (participants 1 and 12) described being aware of the possible risk of liver damage from alcohol consumption, but continued to drink to cope with family issues.

What really kinda kicked it off, well some of it, I've always been a heavy drinker but my wife passed away in 1996 with cancer and I fell into the very bad habit of going down the neck of a bottle, it was a comforter, it took the pain away for a little while but the next day when you wake up, it's all still there and I did go through a bad spell then.
Participant 12, Hazardous Alcohol, Inner City GP, Normal liver scan

Participant's peer group alcohol intake was also important in understanding whether they appreciated that their own alcohol consumption was excessive. Several participants described that their alcohol intake was in keeping with their social group, and so did not consider their alcohol consumption to be hazardous or putting themselves at risk of adverse health consequences.

So talk me through what your alcohol intake was back then before you had the scan?

I went out, had 6-8 pints, might be three times a week, bottle of wine at home now and again, just drank when I felt like it and social, I

thought there's nothing wrong with me, I did, just carried on as everybody else does. Participant 14, Hazardous alcohol, Inner City GP, Liver Cirrhosis

A further source of understanding of participant's personal liver disease risk due to alcohol consumption was opportunistic intervention by the participant's GP during routine appointments. Such appointments resulted in a discussion of alcohol intake, generating awareness of the participant's hazardous alcohol use and subsequently referral for a liver scan appointment.

What were your thoughts on that, about being asked to have the liver scan done?

It worried me, I thought "crikey" and I wasn't quite sure what we'd said in the conversation that had made him feel that I need to because it was part of his general questions to me about lifestyle and "Do you drink?", "yes I drink", I told him how much I drink and then that led onto "I think we'll get you scanned" and I thought "oh, did I say I like a bottle of gin a night?", and it scared me. Participant 20, Hazardous alcohol, Inner City GP, Normal liver scan

2. Experience of liver disease screening

As part of any new screening programme, it is important that the investigations undertaken are acceptable to patients and do not provoke unnecessary distress in their conduct. The following 2 sub-themes discuss the screening experiences for patients of the TE scan appointment, including

understanding and acceptance of the liver disease screening process, positive and negative experiences recalled of having a TE performed, and the immediate understanding of the results at the time of the scan.

a) Acceptability and understanding of screening process

Invitation for the TE scan appointment primarily originated from either the GP or diabetic nurses for participants with type 2 diabetes, and via opportunistic appointments with the GP or letter invitation for participants with hazardous alcohol use. Unsurprisingly, as these are patients who attended the TE appointment, the process of being screened for liver disease in the community setting was seen as acceptable to all participants. However, there were different reasons identified by participants as to why they decided to undergo the TE. Several participants discussed being accustomed to screening procedures as part of their routine diabetes care, and were happy to attend for the TE on the recommendation of the GP team alone.

> ***You didn't feel it was an issue being referred on for this extra test?***
>
> *No, I didn't worry me at all, I just thought right, fine, it's just another thing for me and I'm quite happy to go along and have things checked – because not only that, it's for your own benefit.* Participant 7, Type 2 Diabetes, Inner City GP, Liver Cirrhosis

Related to their prior experience of chronic disease screening, another common reason for TE scan attendance identified by participants with type 2 diabetes was to enable the early detection of a liver problem before it resulted in any significant symptoms.

I think knowing is better than not knowing because if you know something, there may be things you can do to change it and to make it better.

I don't know what other people think but for me, I like to know what's going on and I like to know is there a resolution to this? Is there a way to proceed forward? And I think that's for me a good thing to know. Participant 16, Type 2 Diabetes, Inner City GP, Liver Fibrosis

The invitation for a TE scan came somewhat out of the blue and generated both surprise and anxiety in some individuals with hazardous alcohol use. However, this did not appear to preclude attendance for the TE appointment.

'Cause like when you contacted me, I was quite surprised, I was like "oh where's this all come from?", "what is it with my liver?", but yeah, no, no it hasn't really bothered me. Participant 15, Hazardous alcohol, Inner City GP, Normal liver scan

Recall of information provided prior to the TE appointment was mixed. Several participants had very limited recollection of whether any information had been provided prior to the scan appointment.

Did you get any information, obviously it was about the liver, were you given any information about what to expect?

Not really given anything as to what to expect, I was just told it was going to be a simple scan for a study of the effects of diabetes on the liver, I think she said.

Did you understand what these scans were actually looking for in the liver?

No, to be honest. I've never really thought much about that side of things so you know, I didn't really know what they was actually looking for. Participant 6, Type 2 Diabetes, Suburban GP, Liver Cirrhosis

Others recalled an understanding of the TE device derived from either a leaflet provided prior to the appointment or the explanation provided by the nurses at the start of the liver scan appointment. Knowledge gained included the changes in properties of the liver due to the development of scarring which are detected by TE; this was described correctly by several participants as 'rigidity', 'hardness' or 'stiffness' within the liver.

What kind of information were you given about the scan before you had it done, if any?

Just explained how it worked, the two nurses, they were very good and they explained how it worked and what happens to the test, so they explained it well, what it was measuring; it was the density of the liver, like an ultrasound, so they explained all that and they were very good. Participant 20, Hazardous Alcohol Use, Inner City GP, Normal liver scan

Participants identified a number of positive features of the experience of liver disease screening. Most patients felt that being reviewed at their GP practice, rather than the hospital setting which had been the case with their previous scan appointments for other health concerns, was convenient and allowed attendance outside of working hours. One participant also felt that attendance for liver scans would be improved in the community due to this aspect of convenience.

So you found that very convenient did you?

*I found that a brilliant idea, yes because a colleague of mine has just had it done as well because he said "do I have to go to the hospital?", I said "no", I said "you have it done at your doctor's surgery", which I think is brilliant because a lot of people wouldn't bother coming up here. P*articipant 7, Type 2 Diabetes, Inner City GP, Liver Cirrhosis

It was perfect to be at the GPs and it was good how it suited me because then I didn't have to take time off work to get it done, which is very … it's convenient, so it's not too much disruption to my work profile. Participant 13, Type 2 Diabetes, Inner City GP, Liver fibrosis

Related to the convenience of having the scan in primary care, several participants discussed the quick nature of their TE appointment. The time taken for the appointment was seen as surprising, with a couple of participants comparing the liver scan time favourably to hospital appointments and their usual GP appointments respectively.

It was all done in 20 minutes over and done with and it was not a problem at all, it was probably the easiest scan I've ever had, for anything! When they say "it's done", you think "already?". "It takes a bit longer than this to have an appointment with the GP". Participant 16, Type 2 Diabetes, Inner City GP, Liver Fibrosis

Overall the TE scan appointment was regarded as a positive experience by participants. Furthermore, the TE scan itself was described as a simple and painless procedure by all bar one participant (participant 6). This participant described the scan as an uncomfortable procedure, although later went on to describe the process of having a liver biopsy as comparatively more painful.

At the time, it doesn't hurt but yes, it is quite uncomfortable to have it pushed, your rib cage pushed quite hard but I mean … there's worse things that they can do to you!…. so they had to go in through the side, so I had a little incision in the end.

How did you find that?

That was very, very uncomfortable, that was even worse than the pressure on the ribs. At one point it actually hurt! Participant 6, Type 2 Diabetes, Suburban GP, Liver Cirrhosis

b) Participant interpretation of numerical liver stiffness result

Participants received their TE scan result in terms of a numerical liver stiffness value which was discussed with participants by the nursing staff

during the scan appointment in addition to relevant lifestyle-related advice. Recall of this value by participants during interviews was inconsistent, although did not appear related to follow-up time between the TE scan and participant interview. Approximately half of participants interviewed were still able to recall their exact liver stiffness measurement, whilst several participants did not remember there being a numeric result at all.

> ***But it was more that you remembered that you had a normal result rather than the actual number?***
>
> *Yes, normal-ish but she did mention something, I remember her mentioning numbers but off the top of my head, I can't remember what they were.* Participant 12, Hazardous Alcohol, Inner City GP, Normal Liver Scan

Subsequently, some participants felt that just being told that their scan result was normal or abnormal was enough information to be fed back to them.

> ***Was it particularly meaningful, being told the scan as a number rather than just being told it was normal, did that help you understand what's going on?***
>
> *No, I just think "normal" is the word you're waiting for isn't it?! The numbers don't mean anything though, if you know what the range is that someone is looking for from 1 to 10 and in the middle is normal.* Participant 20, Hazardous alcohol, Inner City GP, Normal liver scan

Other participants preferred a numerical value as the result felt more personal to them, and also provided a baseline for comparison in case further scans were provided in the future.

Did having a score like that mean more to you than just saying it was normal?

Yes, I think to give any state of affairs in numerical value because we're all used to a scale of 1 to 10, we do it all the time, so yes I think that was better because then you've got a starting … because the terms "satisfactory", "normal", "good", "very good", "excellent", they're all subjective, they mean different things to different people but a score is a score, if you have a score of 6.1, it's not 6.2 and neither is it 5.9, it's a definite starting point. Participant 5, Type 2 Diabetes, Suburban GP, Normal liver scan

Several participants did not fully understand what their numerical liver stiffness meant at the time of the liver scan. Although the cutoff of what represented normal and abnormal liver stiffness values was made clear to participants during the appointment, some participants were less certain of how to interpret the severity of abnormal results as the possible ranges and severities of liver stiffness results were not discussed.

What was the impact for yourself of getting the result as a number rather than a, did you find that helpful?

No, because it means nothing, you don't know what scale you're on. 10.1, could be near enough healthy because it could go up to 100, we

don't know but if it only goes up to 15, 10.1 is a bit of a nightmare! You're on the back end of a problem, so without having a context to put it in, it's a bit awkward. Participant 16, Type 2 Diabetes, Inner City GP, Liver Fibrosis

However several participants, through either their own reading or feedback from the nursing staff during the appointment, felt able to use the numerical liver stiffness result provided by TE to make a judgement on the severity of their liver disease. A couple of participants diagnosed with cirrhosis recognised that there was likely to be a significant problem when they received liver stiffness results which were much higher than that which would be expected in a normal liver. Receiving this information appeared to begin the process of these participants contemplating subsequent lifestyle changes prior to being reviewed in the hepatology clinic.

So at the time you had the scan, you said the nurses said the result was 18 …

18.5

18.5 was the result, how did they explain that to you and what did it mean to you at the time?

Well I said, "how's bad that then? What does that mean?". 18.5 didn't mean a thing to me and she says, "We refer you if it's over 8", so I thought "oh it's well over double" so … "I'd better get something done about it", that's it. Participant 14, Hazardous alcohol, Inner City GP, Liver Cirrhosis

3. Initial impact of liver stiffness result

This theme, made up of two component subthemes, highlights the initial impact on participants of their liver stiffness results, and subsequent liver disease diagnoses where relevant. This includes the contrasting emotions experienced by participants with normal and abnormal scan results respectively, their understanding of liver disease following the screening process, and how the new awareness of their liver health made an impact on the initial consideration of lifestyle changes.

a) Generating shock or anxiety

Most participants reported that prior to the liver scan being performed they had an expectation that no liver abnormality would be detected. Expectations of a normal scan was derived from a number of factors, including a prior lack of knowledge regarding their own risk factor for developing liver disease, the absence of previous symptoms which they might attribute to liver disease, and in several participants previously normal liver function blood tests measured by their GP.

> ***What were you expecting the result to be, normal, abnormal …?***
>
> *I didn't, I wasn't sure, I really wasn't sure because I wasn't really getting any pain from that area so I was kind of thinking yeah, it will be all right because a few times I've had a lot of blood tests over the years with my liver and they've always come back fine.* Participant 15, Hazardous Alcohol Use, Inner City GP, Liver Fibrosis

Subsequently, a common initial reaction reported by participants with elevated liver stiffness results was surprise or shock that an abnormality was detected by the scan. Furthermore, some participants went on to report that this resulted in them considering changes that would be needed to their lifestyle to prevent the worsening of their liver problem.

So you were quite shocked?

Yeah, I think maybe that's when, because I was drinking still then … I think maybe that was when I just went, "okay, got to do something now, it's serious". Participant 1, Hazardous Alcohol Use, Inner City GP, Liver Cirrhosis

Further to the liver scan appointment, patients who had elevated liver stiffness results were offered additional investigations following consultation with a hepatologist in order to definitively stage their liver fibrosis and cirrhosis. Following these investigations, patients were subsequently reviewed in the hospital liver clinic to discuss their diagnosis. Participants who were diagnosed with cirrhosis commonly reported significant anxiety generated by learning they had this condition. A particular concern was highlighted by several participants with cirrhosis (1, 2 and 6), who were especially anxious that cirrhosis would progress quickly or result in their premature death.

Because it's how it was explained to me, I sort of understood it better because you know when somebody says liver disease, cirrhosis of the liver, your mind starts working overtime and you think you're going to

be dying soon. Participant 2, Type 2 Diabetes, Inner City GP, Liver Cirrhosis

This anxiety which occurred on learning their unexpected diagnosis of cirrhosis was described by two of these participants to result in them 'switching off' during their initial liver clinic consultation. Subsequently, these participants gained only a limited understanding of what cirrhosis actually meant and the potential consequences of cirrhosis, generating further anxiety. One participant (Participant 2) explained that she was not sure who she could ask questions to regarding cirrhosis outside of the liver clinic environment, and she remained distressed until her next clinic appointment. Additional follow-up appointments allowed an opportunity for participants to ask relevant questions and alleviate these concerns.

Then I was thinking of all really bad, you know, I've got cirrhosis, how big is this cirrhosis on my liver? Is it the whole liver? Is it one lobe? I was asking all these questions but I couldn't ask it to the appropriate person because that person wasn't there…when I saw Dr [Doctor's name] in the clinic, he told me the results of my liver biopsy and because I wasn't aware that he was going to say all this, it just went over my head and then it obviously, afterwards, but I do feel a lot better now since like I say I've been coming here and I've been explained things better. Participant 2, Type 2 Diabetes, Inner City GP, Liver Cirrhosis

Additionally, one participant also reported the anxiety of having a

further significant co-morbidity diagnosed. This resulted in distress for this particular participant in having to cope with a diagnosis of cirrhosis in addition to her pre-existing musculoskeletal and diabetes-related co-morbidities.

> ***One of the things you mentioned was surprise, how did it make you feel being told that you had cirrhosis?***
>
> *After I'd got over the initial shock, I just thought "Oh well, something else I've got to deal with" and it's like anything else, you learn to cope. It's not easy, when I've got so many other things going on anyway, to find out you've got another thing on top was a little bit much! But other than that, as I say you just cope so yes. That's it really.* Participant 6, Type 2 Diabetes, Suburban GP, Liver Cirrhosis

Despite the surprise and anxiety provoked by a new diagnosis of chronic liver disease, two participants (Participants 11 and 19) expressed some relief that they were diagnosed with hepatic fibrosis and cirrhosis respectively. This resulted from a misunderstanding that the elevated liver stiffness result may be due to an underlying malignancy; this concern was alleviated when these participants were informed of their true diagnosis at the follow-up hepatology clinic.

> *While I was waiting for the scan, I read all the information, I could guess from the information on the board that it would be a fatty liver problem, it's just if there's anything else there and when I was told, it was a bit of a relief actually, that it was just fatty liver problems.*

When you say a relief, what were you worried about?

Everybody thinks there might be cancer there sometimes and it was just "oh it's not a cancer, it's that … in another five years or so! Participant 19, Type 2 Diabetes, Suburban GP, Liver Cirrhosis

Overall, marginally elevated liver stiffness results and a subsequent diagnosis with liver fibrosis provoked less anxiety when compared with a diagnosis of cirrhosis. Two participants diagnosed with hepatic fibrosis felt that their liver stiffness result did not represent a significant health issue due to the scan result only being slightly elevated and also not having developed any related symptoms.

You mentioned they told you about the range of results you can get, what were you told about yours?

They told me that mine was above but not serious. That's what they said it was. Nothing to worry about, it was above normal but "don't worry about it". Participant 9, Type 2 Diabetes, Inner City GP, Liver Fibrosis

For participants with normal liver stiffness results, the commonest emotion reported was relief that a significant problem had not been detected. Of these, several participants with type 2 diabetes described the normal scan result as 'one less thing to worry about' as an additional diagnosis was not made subsequent to their pre-existing diabetes and related co-morbidities.

Has having that liver scan made any difference to how you view your health?

Yes, well it's something less to worry about. That's why I go for these annual MOTs and I'll go for a blood test as well in between annual MOTs and yes, it has made me feel better, it was advantageous because it's one less thing to worry about. Participant 5, Type 2 Diabetes, Suburban GP, Normal Liver Scan

b) Increasing awareness of liver-related health and contemplating lifestyle changes

Before the liver screening process, knowledge of liver disease among participants was limited. Following screening, an increased awareness of liver-related knowledge was reported by many participants. Most participants reported learning about their personal risk for liver disease; in participants with hazardous alcohol use this was acknowledgement that their personal alcohol consumption was excessive.

Has the information you've had from ourselves, the liver team and the doctor, meant that you had to change how you view your health and your outlook of your health at all?

Yeah it has, I wish they explained that the drink is affecting me before the scans. I wasn't aware that it was affecting us, so it didn't really matter. Participant 11, Hazardous Alcohol, Inner City GP, Liver Fibrosis

Participants with type 2 diabetes learned that type 2 diabetes and obesity are risk factors for progressive liver disease.

Were you aware of the link between diabetes and liver?

No, I never gave it a thought to be honest, it was not something that ever crossed my mind, that diabetes could give you any serious problems with your liver or kidneys or anything. That was all very new to me, when they asked me to do the study, to go for the scan. Participant 6, Type 2 Diabetes, Suburban GP, Liver Cirrhosis

In participants with normal liver stiffness, new information gained was limited to their own risk of liver disease and the procedure for undergoing TE. Additionally, participants with elevated liver stiffness reported further knowledge gained from appointments with the consultant hepatologist in the community, the participant's own GP and additional personal reading. This included what the diagnosis of liver scarring and cirrhosis meant, functions and regenerative capacity of the liver, and specific lifestyle interventions required to reduce the risk of liver disease progression.

Have you learned anymore about the liver? You said you only really knew about alcohol before....?

Yes, I know what the function of the liver is, you'd think all it was there for was to cleanse things through but I realise what it actually does now. Yeah, I do understand it better because like I say it's how things have been explained to me here as well. I've got a better knowledge

of what the liver is for. Participant 2, Type 2 Diabetes, Inner City GP, Liver Cirrhosis

What kinds of things have you learned since you've had the scan?

I learned a) what the dangers are of it and that if it keeps on worsening, it will go into full cirrhosis and then eventually liver failure and that's it. So if I can stop it worsening … then I can put it off because at 60 if I put it off, it might last me for the rest of my life. Participant 19, Type 2 Diabetes, Suburban GP, Liver Cirrhosis

This new information relevant to participants' liver health facilitated the process of contemplating potential lifestyle changes. Participants who underwent TE and were diagnosed with normal liver stiffness results were made aware of their risk factor for developing liver disease prior to undergoing the scan. In all bar two of these participants this information, in addition to the process of undergoing the scan, resulted in the immediate consideration of needing to make lifestyle changes even though their liver stiffness result was normal.

Is that something that started recently, those days off?

It was the liver scan started things because you think "crikey, I'm going for a liver scan, am I overdoing it?". Participant 20, Hazardous Alcohol, Suburban GP, Normal liver scan

Participants with elevated liver stiffness more commonly discussed the abnormal liver scan result, and subsequent advice from the nursing team and liver specialist, as the initiator of contemplation of lifestyle change rather than the awareness of their risk factor for liver disease alone. Several participants discussed that being told they had an abnormal liver scan was a 'wake-up call' and subsequently prompted them to consider changes that could be made to their lifestyle.

> ***What exactly was the trigger that got you thinking that you needed to do something? Was it the advice you got or was it having an abnormal test or having the biopsy or something else?***
>
> *Having an abnormal test, no doubt about that. I think we all like to think we're perfect …! If there's something wrong and you can do something about it, you're daft if you don't, that's the way I look at it.*
> Participant 9, Type 2 Diabetes, Inner City GP, Liver Fibrosis

Several other participants with elevated liver stiffness required further information in addition to the liver scan result to begin the process of contemplation. The explanation from the consultant hepatologist of the participant's liver disease diagnosis and possible future adverse health outcomes raised their awareness of liver disease and began the process of considering necessary lifestyle changes.

> *I made a promise to you chaps, I don't know if you remember it but I said "I won't stop drinking but I'll certainly cut down and go onto the weaker stuff" or whatever and actually I find the weaker stuff really*

better….. You explained everything, I thought, "I've got to do something about it", is what I was thinking at the time of you speaking to me. Participant 18, Hazardous Alcohol, Inner City GP, Liver Fibrosis

4. Uptake of lifestyle change

This theme provides an overview of the lifestyle changes achieved by participants in the 6 month to 2 year interval between having the liver scan and undergoing interview. The reported role of the liver screening process and TE scan results are described, as well as other important facilitators and barriers to lifestyle changes for both hazardous alcohol use and type 2 diabetes.

a) Lifestyle changes achieved and the role of liver screening

All participants with hazardous alcohol use reported at least some reduction in their alcohol intake during follow up, whilst 5/12 patients with type 2 diabetes reported dietary alteration or increased physical activity following the TE scan. Lifestyle changes were achieved in 5/7 participants with a normal liver scan result and 5/6 patients diagnosed with cirrhosis made a lifestyle change. However, more than half of participants diagnosed with liver fibrosis did not initiate a lifestyle change. The facilitators and barriers to these lifestyle changes are discussed in subthemes 4b and 4c. Some representative examples of participants who did and did not achieve lifestyle changes is shown below:

What are the reasons for that and what difficulties have you had?

It can be a big step. When you work all day, it's not easy to come home thinking, "right, I'm going to have a small portion of this, a small portion of that, because I'm hungry and I want to, I feel like I've been to work all day so I want to have something to look forward to when I come home, if it's a big meal, it's a big meal, sorry but that's the way things are. Participant 13, Type 2 Diabetes, Inner City GP, Liver Fibrosis

Ever reduced that intake before the scan?

Both me and my wife are mindful, we have days off, we make a point of having one, two, if we can three days off just so that we know at the end of the day, we can, we don't feel like we desperately need to have a glass of wine, we have breaks. Participant 20, Hazardous Alcohol, Inner City GP, Normal Liver Scan

…but has it changed how you view your health?

In some ways it has, yes, it's made me want to try and exercise more and try and lose some weight but as I said earlier, I am restricted. Participant 6, Type 2 Diabetes, Suburban GP, Liver Cirrhosis

Of the 5 participants with normal liver scan results who went on to make a lifestyle change, 4 of these individuals managed to reduce their alcohol consumption, and 1 increased their exercise levels in addition, in spite of a normal liver scan. The other participant (participant 8), although not

making any lifestyle changes directly related to his type 2 diabetes, felt compelled to reduce his alcohol intake as a result of the liver screening process.

> ***So you had the liver test done 18 months ago and obviously a normal result was fed back to you, has it changed anything you do?***
>
> *I suppose it did change in a way, I don't drink an awful lot of alcohol but I do drink alcohol and when I looked at it, I seemed to be drinking every day, which I don't do now, I have two days off when I try to drink nothing which is generally okay, unless I'm on holiday, so I've changed in that.* Participant 8, Type 2 Diabetes, Suburban GP, Normal Liver Scan

Several participants with a normal liver scan, reported that the process of undergoing liver disease screening was their primary reason for making lifestyle changes. This was mainly achieved by raising an awareness of the participant's risk of liver disease, and subsequent reflection on their lifestyle choices.

> ***Is that something that started recently, those days off?***
>
> *It was the liver scan started things because you think "crikey, I'm going for a liver scan, am I overdoing it?"…. I think having the scan has changed my attitude to drinking, that's when the breaks probably started as I said to you before, going for that, give us a bit of a wakeup*

call. Participant 20, Hazardous Alcohol, Inner City GP, Normal Liver Scan

A further participant commented on the surprise that her liver scan was normal, as she had assumed her previous alcohol excess had caused damage. This participant still managed to decrease her alcohol intake during the follow up period nonetheless.

I was surprised that everything was fine 'cause it's like, in a way, with the drinking and then taking the pills every now and again and that, it's like … it is kind of abusing the liver isn't it? And they're telling me it's fine so I kept thinking I must have a cast iron one! I was surprised that everything was fine with it and that. Participant 15, Hazardous Alcohol, Inner City GP, Normal Liver Scan

The two participants with a normal scan who did not make a lifestyle change (participants 5 and 17), did not feel the need to make change directly as a result of their liver scan result being normal. They felt reassured by the normal scan result, and therefore saw no need to make any lifestyle changes for their liver health.

So just to clarify, having the liver scan hasn't really changed your health beliefs per se?

No because as I said before, it was a good result, one less thing to worry about, I don't have to worry about my liver. Participant 5, Type 2 Diabetes, Suburban GP, Normal Liver Scan

In total, 13 participants made lifestyle changes following the liver screening process, however only 8 participants had sustained these changes at the time of interview. All bar two participants (both with hazardous alcohol use) reported that they had experienced some difficulties in maintaining their lifestyle changes.

> *It's keeping the enthusiasm up to do it, when you're really overweight, it's hard, it's flipping hard, it's keeping the motivation up to go back and go back and go back, a couple has dropped off already, they're big lads, bigger than me, a lot bigger than me and they ain't turned up the last two weeks, I think you've got to have the motivation to do it, you've got to want to do it ain't you really?* Participant 9, Type 2 Diabetes, Inner City GP, Liver Fibrosis

Some participants had drifted gradually back towards old behaviours, noticed this, and then managed to return to their lifestyle change.

> *I sort of fell into it a little bit and then I've thought, "whoa, wait a minute, you're drifting back again" and stopped and try again and get back on an even keel in the week sort of thing.* Participant 12, Hazardous Alcohol, Inner City GP, Normal Liver Scan

However, for other participants the impact of the liver scan continued and they reported that liver scan itself was the primary reason for going on to make a lifestyle change. In those participants with elevated liver stiffness, the demonstration that they had caused significant damage to their liver was a

continued shock which they felt was directly responsible for causing their subsequent lifestyle changes.

> *Having an abnormal test, no doubt about that. I think we all like to think we're perfect …! If there's something wrong and you can do something about it, you're daft if you don't, that's the way I look at it, I think just try it and see. But it was the test that shocked me into it if you like, it definitely was that.*
>
> Participant 9, Type 2 Diabetes, Inner City GP, Liver Fibrosis

b) Facilitators of lifestyle change

The facilitators and barriers to adopting lifestyle changes reported by patients during the interviews are listed in table 25; those reported by participants with hazardous alcohol use and participants with type 2 diabetes as their liver disease risk factor are listed separately. In addition to the important role of the liver screening process and scan result itself, which was described in the previous sub-theme, the 3 most important facilitators of lifestyle change described by participants were the participant's family, education and support groups and the medical team. These 3 factors are described in more detail below.

Table 25 – Facilitators and barriers to lifestyle change described by interviewed participants		
Risk Factor	**Facilitators**	**Barriers**
Hazardous Alcohol Use	- Abnormal liver scan - Medical Advice - Family - support - Friend/family with cirrhosis - Alcohol services - support - Family – concurrent lifestyle change - Reduction of symptoms when stopped alcohol - Liver screening process - Advancing age - Severe illness e.g. organ failure - Fear of death - Homeopathy - Symptoms of alcohol misuse - Occupation	- Established Habits - Peer pressure - Craving - Family – Stressful relationships - Alcohol helped with sleeping - Lack of awareness of excessive alcohol - Family – bereavement - Medical advice – not believed by patient - Subsequent improvements in liver scan - Occupation – stress
Type 2 Diabetes	- Severe illness e.g. organ failure - Education course – knowledge acquired - Abnormal liver scan - Introducing hobbies - Friend/family with previous cirrhosis - Advancing Age - Education course – motivation for change - Family – concurrent lifestyle change - Medical advice - Liver screening process - Establishing a routine - Making small realistic changes - Free gym membership - Occupation - Feeling better after exercise	- Musculoskeletal disease - Subjective feeling that changes not possible/unrealistic - Lack of symptoms - Normal liver scan - Craving - Changes not reinforced by weight loss - Medications (increasing appetite) - Liver diagnosis not felt to be significant - Fear of Falling - Living alone – no-one to aid motivation - Peer pressure - Previous habits - Lack of instant results - Occupation - Advancing Age - Mental health issues

i) The role of the participant's family

More than half of participants described their immediate and extended family circumstances encouraged them to make lifestyle changes. Firstly, several participants with hazardous alcohol use reported that close family members put pressure on them to reduce their alcohol consumption, either by directly confronting the participant or by the participant reflecting on the possible detriment their alcohol consumption was causing to their family. The result of this both raised the awareness that their alcohol consumption was possibly aberrant, but also highlighted negative aspects of these family relationships which participants actively sought to improve by reducing their alcohol intake.

> *First thing that comes to your mind of course is your family, the wife, kids, grandkids, you know? You think, well, if it is serious, serious, I'm one of these chaps that will say "Yeah okay, I'll abstain from it", I wouldn't touch it, I wouldn't do anything. That's how I felt. I did feel that way. So you think about your family first and not yourself.*
> Participant 18, Hazardous Alcohol, Inner City GP, Liver Fibrosis

Several other participants commented upon their experiences of cirrhosis diagnoses in family members having an impact on their lifestyle choices. In these cases, the relevant family member had symptoms due to liver failure from alcohol misuse, which subsequently moderated either the quantity or type of alcohol which the participant themselves consumed.

> ***Can you tell me a bit more about that?***

She drank vodka and gin a lot, she drank it every day and she didn't eat, yeah, she just died. She lost a ton of weight and died and they said it was liver failure she died of, so basically her liver failed her but she did drink heavily, gin and vodka.

So did it worry you that you might have a similar kind of problem with the liver develop at all?

Kind of but then I looked at it and it's like I don't drink the hard drinks, to me that's hard liquor, I don't drink that stuff unless it's Christmas time, I'm more of a lager person, I drink lager or I used to drink cider but not really them or even wine, I used to drink and that but not really them, only on occasions I drink that kind of stuff. Participant 15, Hazardous Alcohol, Inner City GP, Normal Liver Scan

Another aspect which facilitated a change in lifestyle was concurrent lifestyle changes also being adopted by close family members, particularly the participant's spouse. This resulted in an increased motivation to start and sustain lifestyle changes, and was reported by both participants with hazardous alcohol use or type 2 diabetes.

I did actually cut down a little bit more on the alcohol and try to do more exercise as well, so we are, I've got the wife doing it as well, out running as well and yeah, we both try to do a little more while we still can and we have definitely cut down on the alcohol since then, so yes, it has had an impact. Participant 10, Hazardous Alcohol, Suburban GP, Normal Liver Scan

The opposite was also true, with one participant (participant 7) reporting that not having support from anyone was a barrier to lifestyle change.

How about your activity or exercise at the time, is that something you changed as well?

Yes, I started doing a lot more walking, which I enjoy, I keep saying I'm going swimming but I've not got round to that. I think being on your own, you just need somebody to push you basically, that's what it's about and as I haven't got anybody around to push me, I'm a bit lazy! Participant 7, Type 2 Diabetes, Inner City GP, Liver Cirrhosis

However, the participant's family was not felt to have a universally positive role. Several participants with hazardous alcohol use reported that stress generated by relationships with their close family or bereavement were a significant trigger to increasing their alcohol consumption.

What was it, could you put a finger on what brought you back to drinking after that?

I think it was just problems, life things going off with family and whatnot, just got me down and then I started drinking again. Participant 15, Hazardous Alcohol, Inner City GP, Normal Liver Scan

ii) External agencies – education/support groups

Many of the participants reported interaction with education or support groups, both before and after their liver scan. Several participants with

hazardous alcohol intake had used hospital-based or community-based alcohol services aiming to reduce their alcohol consumption. Their experiences were generally positive, with these participants reporting a reduction in alcohol intake associated with the support process, although alcohol reduction was not sustained in all cases. One participant (participant 1) felt that the support provided by a community based alcohol support service in Nottingham, was vital in helping her to achieve alcohol abstinence.

> *…. February 13th and I did it with [community based alcohol support service], so I had a, is it lithium? I went on a detox and you sort of go there in the day and they give you the pills and an injection and vitamins and you come home at 4 o clock and I just did that and found it so easy.*
>
> *Afterwards, they give you drugs for cravings but I didn't need to take them, I never took them because I just … just clicked.*
>
> ***How important do you think that support was?***
>
> *I think it was vital because it broke the cycle for me, I needed to get out of the house and break that cycle of just having a drink. So it was vital.* Participant 1, Hazardous Alcohol, Inner City GP, Liver Cirrhosis

Participants with type 2 diabetes reported interactions with a number of education and support groups. As reported in a previous theme, most of the participants had taken part in a local diabetes education course at the time of their diagnosis, which had a positive impact in particular on their dietary choices. Following the liver scan, several participants took action by

joining a weight loss support group. A particular benefit perceived by joining such groups was that it provided an environment which motivated the participants to maintain the lifestyle changes they had made. This was achieved by either providing specific weight loss targets for the participant, or the success of other members of the group reinforcing the participant's lifestyle changes.

> *The women down there as well, I know one of them, she goes up the club, you think "oh, somebody you know" but you soon get to know people, I was talking to some of the people there, some have lost 3 or 4 stone and they've been going about a couple of years now, if you hit your target, it just carries on, it rolls on so it's quite good, it's something there to motivate you.* Participant 9, Type 2 Diabetes, Inner City GP, Liver Fibrosis

iii) The role of the medical team

The medical team were perceived by participants to have additional roles to aid lifestyle change, further merely to providing the participants with their liver scan result. Several participants, more commonly those with hazardous alcohol use, considered the medical team to be figures of authority with regards to lifestyle choices; if the GP or nursing team raised concerns about the participant's lifestyle then this would lead to them more seriously considering the need to adopt the suggested changes.

Did lifestyle advice from the GP or the nurses have any impact on the changes you've made or was it a decision you made yourself?

Probably they … they have probably shown a little bit of concern over it, in case you sort of did drink too much and just telling you what you should maximum drinking and everything so yeah, that has made an impact as well, with them saying, you think they obviously know what they're on about so you do take heed a little bit when a professional tells you like that, so yeah that has … put a bit of impact in as well. Participant 10, Hazardous Alcohol, Suburban GP, Normal Liver Scan

The medical team also signposted participants to education courses and support groups, which would be able to provide additional help for patients to make lifestyle changes.

Have you had much support from your GP, with regards to your drinking?

Oh yeah because even he said that that's one of the reasons why I went self-referring anyway because my GP said it would be best to go back to Last Orders and they've always said just go in and that, and it's sorted. Participant 15, Hazardous Alcohol, Inner City GP, Normal Liver Scan

c) Barriers to lifestyle change

A greater number of barriers to lifestyle change were reported in participants with type 2 diabetes compared to hazardous alcohol use. Moreover, reported barriers in type 2 diabetes were more commonly related to the participant's perceived ability to perform exercise rather than dietary changes. The 3 most important perceived barriers to lifestyle change were the participant's perception of being able to make further lifestyle changes that the liver disease diagnosis was not a serious problem due to a lack of symptoms in the participant and that lifestyle changes did not provide instant results. These are described in detail below.

i) The perception that the participant cannot make further lifestyle changes

Although all of the patients with hazardous alcohol use made lifestyle changes following their liver scan result, 7 participants with type 2 diabetes did not make lifestyle changes. The most common reason reported for participants struggling to make a lifestyle change was that they simply did not feel it was possible to do so, a belief which had a couple of components.

Type 2 diabetes is a multisystem disease, and most participants with type 2 diabetes reported that they suffered symptoms from musculoskeletal comorbidities, which affected their ability to perform exercise. Subsequently, when these participants were informed of the need to increase their activity in order to lose weight, they did not feel that this was an aspect of their lifestyle which they could change and were therefore unable to adopt this advice.

Exercise, we were talking about going swimming but that's no longer physically possible for me because my hands are gone, my shoulder's gone and my back hurts. It's not physically possible anymore and that's the least impact exercise I could do. Participant 16, Type 2 Diabetes, Inner City GP, Liver Fibrosis

It was common for participants to report lifestyle changes having been made at the time of their diabetes diagnosis, most commonly with regards to dietary changes aiming to reduce their dietary sugar intake. Upon subsequently being diagnosed with liver fibrosis or cirrhosis following the TE scan, several participants experienced frustration at the lifestyle advice given by the liver team. They did not feel there was any room to manoeuvre with regards to making additional lifestyle changes, and therefore their lifestyle subsequently remained unchanged.

Has having had the liver tests and of course a positive scan, changed how you view your health at all?

Not really because what can I do? I can't do any more than I'm already doing. Therefore I can't change any more than I'm doing now and it's just the exercise that I've got to try and keep up with, as soon as my back's better. Participant 2, Type 2 Diabetes, Inner City GP, Liver Cirrhosis

ii) Diagnosis not serious as absence of symptoms

As discussed in a previous theme, the presence of symptoms was a key determinant to participants of whether they felt healthy or unhealthy. In

those with hazardous alcohol use, symptoms also raised awareness to participants that their alcohol use was excessive. Even when diagnosed with a liver abnormality following the TE scan or liver biopsy, several participants did not consider a lifestyle change as they did not feel the diagnosis warranted doing so. The lack of symptoms, or immediate severe consequences such as death, meant these participants chose not to follow lifestyle advice from the medical team and remained in status quo.

> ***Was that part of the reasoning? That it wasn't a major abnormality found, therefore you didn't feel you needed to make a change to your lifestyle?***
>
> *Yeah, basically, it wasn't so "you've got to do this or this will happen", it's like, "figures are not that high, it would be nice if you could lose the 10%", it wasn't like "you've got to do it otherwise this is going to happen to you", basically "you'll die".* Participant 13, Type 2 Diabetes, Inner City GP, Liver Fibrosis

All of the participants who had not made any lifestyle changes following the liver screening process were asked what would be required in order for them to be empowered to make significant changes. All responded that it would require a severe illness, such as an organ failure or significant vascular event, to result in lifestyle alterations. On further questioning, a diagnosis of cirrhosis was felt by most to be a significant enough health issue to fall into this category.

So let's say and this is obviously a bit hypothetical, you'd been told you had advanced liver scarring or cirrhosis of the liver …?

I would crap myself, to put it bluntly. And then I would seriously have to look at my lifestyle and see if I could turn it around because I know the liver is self-healing but it's only up to a certain point and beyond that point, it's game over. Participant 13, Type 2 Diabetes, Inner City GP, Liver Fibrosis

iii) Lifestyle changes not an instant fix

An important aspect which limited the sustainability of lifestyle changes which were made by participants with type 2 diabetes was that when patients made changes, they did not provide a short term fix; they required a long term commitment in order to see significant alterations to the participant's weight. Even when the barriers to making changes in lifestyle had been overcome, persisting with changes despite limited initial results was seen to be hard work.

…So I've cut all the cheap stuff out but most of the stuff is reduced portions and stuff like that, not snacking in between meals, it's basic stuff really isn't it? But you know, you think "will it work?" but it does over time, it works doesn't it? It's not instant but you know what I mean, some people want an instant fix but you don't get one do you? It works for me anyway. Participant 9, Type 2 Diabetes, Inner City GP, Liver Fibrosis

As well as the difficulty experienced due to the effort required to make and sustain lifestyle changes, several participants expressed disappointment that over time their improved diet and exercise did not result in significant weight loss. These participants found this lack of weight loss disempowering and did not feel encouraged to subsequently maintain their lifestyle changes.

> *But I also found that if I decided I won't eat chocolate for a month or I won't touch a packet of crisps, it always seemed that I'd not lost any weight so it's no encouragement if you see what I mean.* Participant 4, Type 2 Diabetes, Suburban GP, Liver Fibrosis

5. Repeating liver disease screening in the future

This final theme explores participant's thoughts on whether they would engage in future opportunities to screen or survey for liver disease based upon their experiences of liver disease investigations as part of the Nottingham Community Liver Study.

There was unanimous agreement from participants that they would agree to undergo repeat TE examinations, and most participants agreed that an interval of 3-5 years for further screening of liver disease would be reasonable and acceptable to them. The reasons suggested for considering this were different for patients with normal liver scans compared to those with abnormal scans. Participants with abnormal liver stiffness provided two important reasons for wanting to undergo repeat TE measurements. The first reason was to keep a check on the liver in order to ensure that no worsening of their liver disease had occurred.

I definitely would like to know because there's no feeling there and, well there is when you're in your late stages of damage, liver damage, I know that but to me there isn't and there's no tell-tale signs that it's getting worse and I don't want that to happen. Participant 3, Type 2 Diabetes, Suburban GP, Liver Fibrosis

The other main reason for participants wanting repeat TE was to detect if improvements in lifestyle had resulted in subsequent improvements in liver stiffness in order to reinforce the lifestyle changes which had been made.

You'd clearly be keen to have the scan again, what reasons are there for that?

*To check, to see if these reductions we've made, my wife and me have made, has an impact for the positive side or is it still the same? Because there must be people out there similar to me, wanting to know or trying to be in control, that's the reason why I would think so but…*Participant 18, Hazardous Alcohol Use, Inner City GP, Liver Fibrosis

One participant with abnormal liver stiffness who did not consider lifestyle changes despite his liver fibrosis diagnosis (participant 13) suggested that any deterioration in his liver condition in the future may be the precursor to him finally considering and engaging in lifestyle changes.

is repeating the liver scan at an interval of 3 or 5 years later, to see how people's livers are getting on, is that something you'd be interested in having done?

Yes I would, yes. Because then if it's going downhill then it might be a bit of a wakeup call, depending on the severity of when the test was carried out, to when the test is repeated, depending on what the figures are, it might be the kick I need to … do something about it! Participant 13, Type 2 Diabetes, Inner City GP, Liver Fibrosis

Participants with normal liver stiffness still felt it would be important to have a follow up liver scan, despite no abnormality being detected on their initial scan. The main reason reported for wanting additional scans was that participants were keen to ensure that no new abnormality had developed in their liver in the intervening period.

….every 3 or 5 years, I think it would be good because then you can monitor and if it is getting any worse…..you do your bowel cancer every 3 years and all of that, I think this would be a good thing to do the same every 3, 5 years, just to make sure in 5 or 6 years, you're not getting any problems. Participant 10, Hazardous Alcohol, Suburban GP, Normal Liver Scan

Discussion

The rise in population alcohol consumption, obesity and related type 2 diabetes have been key in increasing cirrhosis incidence and mortality. Improving patient's lifestyle choices, and therefore eliminating the individual's

risk of progressive liver fibrosis, is likely to significantly improve this trend. Adoption of lifestyle change following the diagnosis of liver disease is inadequate overall, however few qualitative studies have examined the experience of patients with chronic liver disease following diagnosis. Most of the 13 studies reported in a recent synthesis of qualitative liver disease literature focused upon less common aetiologies such as the autoimmune liver diseases, and patient experience of the liver transplantation process(244). The current study therefore represents one of the first qualitative studies to report the patient experience of investigation and management of common lifestyle related chronic liver diseases (ALD and NAFLD) in either primary or secondary care. Moreover, the study provides novel insight into the experience of participants undergoing liver disease screening in the community using a novel technology and subsequent engagement with recommended lifestyle interventions.

Key Findings of the study

The results of this qualitative interview study suggest that screening of an at-risk population in the community for risk of chronic liver disease is acceptable to the patients undergoing study. Most participants reported their experiences of the liver screening process as positive, with negative comments of the TE scan itself limited to mild discomfort in one patient and failed liver stiffness acquisition in another. Complimentary comments discussed the convenience of having the TE scan in primary care, the speed of the appointment (including receiving diagnostic results and lifestyle advice during the same consultation) and the non-invasive nature of the TE scan,

particularly compared to more invasive tests such as a liver biopsy. For any screening programme, participant acceptance of the investigation is crucial; therefore these findings support the use of screening for liver disease using TE on a larger population.

A further important finding is that prior to liver disease screening, participants' knowledge of their own risk factor for liver disease was poor and was a contributor to their previously adverse lifestyle choices. Whilst knowledge of excessive alcohol use as a cause of liver disease was reported by most participants, their own alcohol consumption was considered as not hazardous on the basis of absence of symptoms and 'the norm for their peer group' rather than recommended safe alcohol consumption guidance. Furthermore, knowledge of obesity or type 2 diabetes as a cause for liver disease was poor, and seemingly not addressed previously by advice from either healthcare professionals or education courses for type 2 diabetes. Subsequently, participants' knowledge of their risk was an important contributor towards making important lifestyle changes to reduce their risk of future adverse health. Education of patients with hazardous alcohol use, obesity and/or type 2 diabetes at a primary care level regarding their risk of progressive liver disease requires improvement, and is one area which may improve liver disease mortality in the United Kingdom.

This study explored the facilitators and barriers to lifestyle changes in participants with hazardous alcohol use or type 2 diabetes who underwent liver disease screening in primary care. The majority of interviewed patients reported initiating lifestyle changes in the intervening period between their TE

scan and the follow-up qualitative interview. Reduction in alcohol intake was more readily reported as a lifestyle change than altered diet or increased physical activity. However, nearly half of participants who made lifestyle changes had been unable to sustain these during the follow-up period (when interviewed 6-24 months after the TE appointment).

Several factors were reported to be key determinants of whether participants adopted or persisted with lifestyle changes. Important facilitators included the participant's family (providing important support and motivational roles), raising awareness of the participant's risk of future adverse health from their lifestyle behaviours, and a diagnosis of liver disease (in particular, the shock associated with a diagnosis of cirrhosis). Barriers to lifestyle change were more readily reported by participants with type 2 diabetes. These included whether participants felt the lifestyle changes were feasible (particularly in view of related musculoskeletal co-morbidities, and previous dietary changes adopted at the time of diabetes diagnosis), the absence of symptoms related to liver disease making the patient feel subjectively that they remained 'healthy' despite in some cases a new diagnosis of clinically significant liver disease, and the lack of instant weight loss from lifestyle changes not reinforcing the lifestyle decision. Clearly, an individual's adoption of lifestyle change was a complex interaction of these aforementioned facilitators and barriers. The deciding factor appeared to be the impact of raising awareness of the participant's risk factor for adverse health or liver disease diagnosis, and whether the individual

perceived this of enough significance to overcome their personal barriers to lifestyle change.

Comparison with other studies

Utilising TE as a liver disease screening tool seemed to have potential for facilitating the adoption of lifestyle changes. Although, there are no prior studies examining the impact of numerical liver stiffness readings on patient behaviour per se, there are limited data on the impact of liver biopsy results and future behaviour.

A previous retrospective French study of 300 inpatients with alcohol withdrawal showed that although the subgroup undergoing liver disease stratification with liver biopsy were significantly less likely to achieve abstinence at 1 year, the biopsied patients with more severe liver disease scarring were less likely to relapse at 3 months and 1 year post hospitalisation(261). Due to the retrospective nature of the study, it is not possible to confirm a causative link between liver biopsy results and alcohol consumption. More convincingly, randomised studies from the smoking cessation literature have demonstrated that numerical biomarker feedback increases lifestyle advice uptake by demonstrating physical damage that patients have caused to themselves (240, 241).

In the current study, the patient preference for a numerical versus categorical result for liver stiffness was variable. Some patients found the numerical result fairly meaningless as they did not fully understand the context of the result, whilst some could not recall the figure. However, several participants found feedback of numerical liver stiffness more useful,

and particularly in those with high results suggestive of significant liver damage the liver stiffness result itself immediately began the patient's contemplation of need to change. Feedback of a numerical elevated liver stiffness results proved somewhat of a double edged sword however. Whilst results which were significantly above normal generated short term shock and anxiety which resulted in participants considering lifestyle changes as discussed, there were instances where less severe liver stiffness abnormalities were perceived as 'just abnormal' and so nothing to worry about. Feedback of liver stiffness results to patients could be improved by ensuring a clear explanation of how the result relates to the degree of liver scarring, whilst stressing the possible future implications of not addressing their risk factor for progressive liver disease. To formally evaluate the impact on future patient behaviour of numerical liver biomarker results, a 3 armed randomised controlled trial comparing categorical versus numerical feedback of liver stiffness results versus standard care should be considered in the future.

The phenomenon that participants were unaware of their risk factor for liver disease is not necessarily surprising. In their qualitative interview study of healthcare professionals who deliver brief intervention advice for alcohol, Rapley et al demonstrated that even healthcare providers who performed brief interventions for alcohol were uncertain of what constituted 'at-risk' alcohol intake, resulting in a reduced confidence to provide alcohol consumption advice to patients(262). This is an area where future public

health campaigns aiming to improve general population knowledge of hazardous alcohol consumption could provide clarity.

Importantly, most participants in the current study considered hazardous alcohol use as the only cause of liver disease. A striking finding was that knowledge of obesity and type 2 diabetes as causes for liver disease were extremely poor. This lack of knowledge is likely to have resulted from the absence of liver disease education during routine diabetes consultations and support courses, which is in keeping with previous studies describing poor primary care health professional knowledge of NAFLD. In an online survey of 56 Italian GPs, only 36% would consider screening their diabetic patients for liver disease(263). In a further questionnaire study of 100 non-liver specialist doctors in Australia, fewer than half of participants knew that NAFLD was not associated with excessive alcohol consumption and 71% had never referred a patient to hepatology services with suspected NAFLD(264). An associated benefit of liver disease screening in the current study was that it provided an opportunity to raise the individual's awareness of their risk factor for liver disease. Many participants in the current study reported that the increased awareness of their health, and knowledge gained about liver disease, was one of the facilitators of adopting lifestyle change. The lack of knowledge regarding NAFLD could be addressed by both national public health awareness campaigns targeting patients, and related training of GP and diabetes education service providers.

Lifestyle change uptake in participants with chronic diseases such as type 2 diabetes is a notoriously difficult area. A large cohort of 2,500

participants with type 2 diabetes in Eindhoven made no significant improvements in activity level, weight or HBA1C levels despite undergoing nearly 3 years of a structured diabetes management programme in primary care(265). Understandably, a large number of previous qualitative studies have evaluated the facilitators and barriers to lifestyle change in participants with either type 2 diabetes or other high cardiovascular risk states in order to determine the factors which encourage and discourage lifestyle changes in these patients. The current study reports a wide range of facilitators and barriers to lifestyle change in participants with type 2 diabetes stratified for their risk of liver disease in primary care.

The key facilitators to lifestyle change reported in the current study were the participant's family, external support and the liver screening process itself. The participant's family had numerous roles, including encouragement of the need for lifestyle change and making concurrent lifestyle changes themselves to aid participant motivation, which were both previously reported in a large qualitative synthesis of 22 qualitative studies interviewing participants with high cardiovascular risk(266). Likewise, the importance of the medical team and external support groups to enhance participant's knowledge of their type 2 diabetes and provide ongoing motivation to sustain lifestyle change has been reported previously(266-268). Facilitative phenomena of liver disease screening associated with lifestyle change uptake, including knowledge gained by the liver screening process and the impact of a diagnosis with liver disease, represents a novel finding which requires further study. Several important facilitators to lifestyle change

reported in previous qualitative literature were not reported by participants in the current study, including the impact of self-management(269), the enjoyment gained from pursuing exercise(267) and the social and religious significance of food(270). This may be due to these prior studies focussing on the facilitators to lifestyle change alone and therefore exploring the topic in more depth, or differences in participant demographics between studies.

In the current study, more barriers to physical activity were reported than dietary changes in participants with type 2 diabetes, in keeping with the previously published qualitative literature(266, 271). Participants in the current study readily reported changes to their diet made at the time of their diabetes diagnosis, but significant barriers to exercise were identified. Previous questionnaire studies of participants with type 2 diabetes have shown that reported exercise levels amongst this group are low, with up to two thirds undertaking no routine moderate or strenuous physical activity(238, 272). Co-morbidity has been commonly reported in previous studies as a barrier to exercise(266, 267, 271), and most participants in the current study reported musculoskeletal co-morbidities having at least some impact on the amount of physical activity that they were able to undertake. A novel finding in the current study is that participants with type 2 diabetes felt that they had minimal room for manoeuvre in terms of adopting further lifestyle changes in addition to those already made at their diabetes diagnosis. This caused some anxiety and frustration, particularly in those participants given a new diagnosis of liver disease who recognised the importance of lifestyle change but felt unable to do so. Small, realistic lifestyle changes which participants

felt were relevant to them seemed most well received by participants, although this requires an improved focus on individualised lifestyle advice rather than blanket recommendations for all with type 2 diabetes. Clearly, optimising physical activity in NAFLD participants with or without type 2 diabetes remains a challenging topic, and remains an area largely unaddressed in the qualitative literature.

Many of the facilitators and barriers reported by participants with type 2 diabetes were also raised by those with hazardous alcohol use. Again, the important impact of family and external support agencies to both encourage action and aid motivation for change were seen as the key facilitators to alcohol reduction as has been previously reported(273, 274). Although all participants reported at least some reduction in alcohol consumption, the interview sample was small and doesn't reflect findings of metaanalyses of brief interventions for alcohol misuse in primary care(132, 133). In the United Kingdom, liver disease screening using a novel blood biomarker in 9 primary care centres has been previously reported in the ALDdeS study(228). Subsequently, the experiences of 30 participants were reported as part of a qualitative interview substudy. One interesting observation was that participants in the 'low risk' blood result group were unlikely to change their drinking behaviour and were in effect given a 'green light' to continue drinking. Amongst the hazardous alcohol users, this phenomenon associated with a normal biomarker result was not confirmed in the current study; only one participant reported the reinforcement of her drinking behaviour due to a normal liver stiffness, but subsequently reduced her reported alcohol

consumption nonetheless. Indeed, simply raising the participant's awareness of their alcohol consumption being abnormal was enough to trigger a reported reduction in alcohol consumption even in those with normal TE scan results. Whilst encouraging, confirming that normal biomarker results do not result in increased alcohol consumption in randomised controlled screening trials would increase the confidence in population liver disease screening.

Relevance of work to theories of behavioural change

An important part of this qualitative research study regards discussion with the interviewed patients of the lifestyle changes adopted following liver disease stratification, the reasons for these changes and the facilitators and barriers which they identified as relevant to lifestyle change in their individual circumstances. Models of behavioural theory, of which there are a large number, therefore have a significant relevance to the study findings. These models are underpinned by assessing and understanding an individual's readiness to act upon and adopt a new behaviour change.

One such model, which has its groundings in lifestyle-related behaviour change, is the Transtheoretical Model (TTM). TTM is a construct which describes the adoption of behavioural change as 'a process involving progress through a series of stages' and was originally devised in the US by Prochaska and colleagues (275). In brief, the 5 stages which are fundamental to TTM are:

i) Precontemplation – the person is unaware of the need to change, or does not intend to embark upon a new behaviour.

ii) Contemplation – the person is beginning to recognize that their behaviour may be problematic or may have adverse health consequences.

iii) Preparation – the person takes preliminary steps to change their behaviour and they are typically ready for action within several months.

iv) Action – the person has undertaken a behavioural change within the last 6 months.

v) Maintenance – sustaining lifestyle changes for at least 6 months, although this stage often requires up to 2 years

There are also 10 processes of change which have been identified which are paramount to progression through the model, many of which are shared between several stages. TTM also recognizes the importance of decisional balance (weighing up the pros and cons of the situation, the balance of which changes as patients advance through the model). Moreover, TTM recognizes relapse i.e. recycling to an earlier stage within the model and resuming prior behaviours. Several formal research studies have been undertaken, including in weight loss management relevant to this thesis, however a recent Cochrane review of 3 low quality studies showed no significant difference in weight loss targets comparing intervention and placebo(276).

As already discussed, in the current qualitative research lifestyle behaviour differed both in regards to patient risk factor and final liver disease-related diagnosis. The full range of behavioural change was

subsequently reported in the follow-up period between TE appointment and interview. The process of screening itself, and the TE scan result, were discussed by patients as factors which contributed to consideration and uptake of lifestyle change. Using the TTM as an example, this included movement of patients out of the pre-contemplation and contemplation stages to action both by awareness of their risk of liver disease and demonstration of damage to the liver due to their previous lifestyle choices. This qualitative study therefore provides preliminary evidence that TE may have a role in patients initiating and maintaining lifestyle changes further to lifestyle advice. TE may therefore be a beneficial adjunct to pre-existing structured interventions such as Brief Intervention advice for alcohol misuse and Cognitive Behavioural Therapy. For example, in addition to changes achieved by liver disease screening and initial TE result, serial TE readings may be used as part of a structured intervention as a feedback mechanism for patients. Demonstrable improvements in liver stiffness measurement during interventions may positively reinforce patients' lifestyle changes, whilst demonstration of deterioration in liver stiffness may help to tackle behavioural relapse. However, few studies have reported serial TE scans in such a manner during lifestyle change, and to my knowledge no studies have formally used liver stiffness measurements as the intervention or adjunct to lifestyle change. Such studies are necessary before formally recommending the use of TE outside of cross-sectional liver disease diagnosis.

Strengths and weaknesses of current study

Given its high prevalence in the general population, NAFLD is a surprisingly understudied diagnosis in the qualitative literature. The current study is therefore novel and reports similarities and differences between the screening experience, diagnosis and lifestyle change uptake of participants with risk factors for ALD and NAFLD.

Interviewing participants 6 months to 2 years following their TE scan importantly allowed exploration of the medium term sustainability of lifestyle changes made by participants whilst limiting recall bias from too large an interval between TE scan and interview. A further strength is that several pre-defined co-factors (GP surgery location, liver disease risk factor and liver disease diagnosis) were used to select participants for interview. This enabled a varied selection of participants to be interviewed, facilitating a diverse description of the phenomena whilst remaining representative of the participants undergoing liver disease screening. Furthermore, participants undergoing TE were selected on the basis of their risk factor for liver disease alone, and were invited from socioeconomically distinct primary care locations in Nottingham. Therefore, the study population are likely to be generalizable to most urban and suburban general practice regions within the United Kingdom.

There are several limitations to discuss from the study however. Firstly, as discussed in the methods section, the researcher had met those participants with abnormal liver stiffness in a single community liver disease clinic. It is possible therefore that the researcher presence may have

impacted the participant's responses, in particular leading to overstating of their achieved lifestyle changes, but also potentially limiting the report of negative experiences of liver disease screening. Whilst it must be acknowledged that this potential bias was not completely eliminated, measures were taken to minimise the impact on participant's interview responses. This included an explanation to the participants that interview transcripts would be anonymised, and importantly, the participants were able to choose the location of the interview, with the majority occurring at the participant's home. Furthermore, the reliability of data collection and analysis were optimised by derivation of the interview guide and dual coding of transcripts by the researcher's supervisor who was independent from the Nottingham Community Liver Study.

Secondly, the interviewed population was relatively small at 20 participants. However, data analysis occurred concurrently with new interviews, and this represented the point at which data saturation of themes was achieved.

Thirdly, the age range of interviewees was relatively narrow (40-71 years). However, this reflects the decades where people are most at risk of developing clinically significant liver disease(24). Moreover, less than 10% of participants who underwent the TE scan were aged 18-39 years, therefore the interviewed patients remain representative of the screened population as a whole. It is possible nonetheless that interviewing younger patients may have altered the experience of phenomena under study.

Lastly, it was not possible to interview participants who refused to undergo screening with TE, as ethical approval was only granted to consent participants for interview at the time of their liver scan. As only approximately 50% of patients underwent TE from the population at risk, exploring the barriers to liver disease screening itself in order to optimise the detection of significant liver disease in the community is important and should be addressed in future studies.

Summary

In summary, undergoing TE to screen for liver disease was acceptable to participants and was reported to directly result in positive lifestyle changes. These findings suggest benefits of population-based liver disease screening in addition to merely earlier diagnoses. Although knowledge of harmful alcohol use as a cause for liver disease was reported by most participants, the knowledge of type 2 diabetes and obesity as a risk factor for liver disease was poor. This is an extremely worrying finding as NAFLD will soon become the leading cause of liver disease in developed nations. Education courses and public health interventions enhancing knowledge of the liver-related consequence of obesity and type 2 diabetes in both patients and healthcare professionals is urgently required. Several participants reported that liver disease screening itself had a positive impact on lifestyle intervention by improving the knowledge and awareness of their health. Although lifestyle changes were achieved by all participants with hazardous alcohol use, participants with type 2 diabetes reported significant barriers to physical activity in particular which limits progression into the

action phase of change. Further qualitative research of participants with NAFLD is vital to ensure relevant lifestyle interventions can be designed to optimise healthy lifestyles in this patient group who are high risk of adverse cardiovascular and liver-related outcomes.

Chapter 6: Conclusions

Key Findings

The prevalence of cirrhosis and subsequent liver-related mortality has increased significantly in recent decades. Fundamentally flawed primary care liver disease investigation algorithms focus on insensitive tests (liver function blood tests), meaning many cases of liver disease are diagnosed late when patients have symptoms of decompensated cirrhosis. This late detection also makes a significant contribution to rising liver disease mortality. The research presented in this thesis studies a new investigation pathway for detecting lifestyle-related chronic liver disease in a United Kingdom primary care setting. This differs from traditional algorithms by investigating patients with defined risk factors for liver disease irrespective of liver blood test results using a community-based testing with Transient Elastography (TE). The research had several aims, the key findings of which are discussed below:

i) To perform a systematic literature review of studies which have employed screening for ALD and NAFLD in a community setting and evaluate the diagnostic performance of non-invasive markers in this specific context.

The systematic review was performed to gather the evidence of liver disease screening in a community setting, detect bias and inadequacies in previously performed study, and use the gathered evidence to contribute towards generation of an evidence based investigation pathway for study in UK primary care for my research. The systematic search of the literature identified 18 studies which screened the general population, or those with

defined risk factors for alcoholic liver disease or NAFLD, for liver disease using non-invasive biomarkers. The main limitation identified was the diverse definition of risk factors, index tests and diagnostic thresholds utilised within the individual studies. Therefore it was clearly not possible to metaanalyse the data or generate a 'one size fits all' pathway for primary care. However it was possible to draw some preliminary conclusions from the data collected.

In the identified research, the most studied index tests were TE, Fibrotest and the NAFLD fibrosis score. TE was the most extensively validated in primary care; 10 studies were identified which examined patients using TE, and 4 of these studies demonstrated liver biopsy data. Although these studies had selection bias as not all patients, or indeed all patients with high index test results, underwent liver biopsy, a high positive predictive value for fibrosis was demonstrated. For example, in the study by Roulot et al(155) used a liver stiffness threshold of 8 kilopascals and of those undergoing liver biopsy 26/27 had any liver fibrosis, and 9/9 had cirrhosis above a threshold of 13 kilopascals.

The systematic review confirmed that diagnosed chronic liver disease prevalence is greater than previously recorded by using newer index tests. The observed liver disease prevalence data in unselected populations were significant liver fibrosis in 6.9-12.8% of patients, advanced liver fibrosis in 0.9-2% and cirrhosis in 0.1-1.7%. Moreover, a large number of cases of chronic liver disease had normal transaminase levels and would therefore be missed by standard investigation algorithms. ALT levels were reported in 9 studies; using commonly utilised laboratory thresholds up to 87.5% of

patients with NAFLD or ALD had normal ALT levels, and even using low thresholds 26.5% and 40% of liver disease cases still had normal ALT levels. These findings highlight the need for an alternative approach to be utilised and further studied in primary care within the United Kingdom.

ii) To assess the feasibility of a community diagnostic pathway for detecting ALD and NAFLD within the United Kingdom healthcare system, and quantify the amount of significant liver disease that is detected using this approach.

Using the aforementioned systematic review and data from the secondary care literature, an evidence based investigation pathway for use in Nottinghamshire primary care was defined. Rather than purely investigating patients with abnormal liver function blood tests, the focus was on defined risk factors for chronic liver disease (hazardous alcohol use, type 2 diabetes and raised ALT level with negative serology). The investigation pathway was piloted in 2 distinct primary care areas; 2 suburban general practices, and a modified pathway without a blood biomarker step in 2 Inner City general practices. Overall a primary care population of 20,868 patients were risk stratified using this approach.

Importantly, the investigation pathway was feasible to implement in the studied practices over a 2 year study period. Overall attendance for investigation was 45%, but varied significantly by risk factor. For example in suburban practices 91% of patients with type 2 diabetes and 38% with hazardous alcohol use attended for the simple blood test. Therefore, relatively robust conclusions about liver disease diagnoses in type 2 diabetes

can be made, but not so with hazardous alcohol use. Attendees for investigation were older and more likely to be male as would be expected with population screening studies. Of 909 patients undergoing TE, 91% had the scan performed in the community setting. Liver stiffness was successfully measured in 98% and reliable measures were obtained in 95%. Therefore, TE was a suitable investigation to use in primary care and a strategy of hospital scans only in those with failed community acquisitions or high body mass index (>35kg/m^2) was successful. Importantly TE was an accurate tool to utilise; of 25 patients having biopsy in suburban practices, 20 had liver fibrosis and the other 5 had steatohepatitis, indicating a greater risk of progressive liver disease.

Using this investigation pathway, a significant amount of previously undetected liver disease was diagnosed. A practice database search identified 23 known cirrhotics pre-study. During the study period, 27 new cirrhosis cases were diagnosed (equivalent to 3% of all scans performed) thereby more than doubling the diagnosed cirrhosis prevalence at these practices. Using previous population data from the UK for comparison(20), the cirrhosis prevalence in this study of 239.6 cases per 100,000 (95% CI 173.3-305.9) is more than three times previous estimates. Diagnosed cirrhosis prevalence in type 2 diabetes was at least 2% and 32% of these patients had elevated liver stiffness. Using ALT laboratory cutoffs analysed in suburban practices, the majority of cases had normal ALT, including 72.4% of those with elevated liver stiffness measurement, 60% with biopsy proven fibrosis and 90.9% of cirrhosis diagnoses.

iii) To explore which risk factors and fibrosis biomarkers yield the highest prevalence of significant liver disease diagnoses.

Obesity and type 2 diabetes were the main risk factors underlying diagnoses of clinically significant liver disease. Only 41% of diagnosed cirrhosis cases (11 patients) had hazardous alcohol use as a liver disease risk factor, and of these only 3 patients had hazardous alcohol use as their sole risk factor. Body mass index measurements and obesity were significantly associated with new liver disease diagnoses and patients with elevated liver stiffness and cirrhosis had significantly higher BMI measurements than those with normal liver stiffness. Overall 61% of patients with elevated liver stiffness and 82% with cirrhosis were obese. Obesity significantly increased the risk of diagnosed cirrhosis in patients with hazardous alcohol use (odds ratio 5.6) and type 2 diabetes (odds ratio 9.4) and strikingly 13.3% of patients with all 3 of alcohol, type 2 diabetes and obesity were diagnosed with cirrhosis. This was significantly greater than, for example, non-obese patients with type 2 diabetes (0.7% cirrhosis prevalence) and non-obese patients with hazardous alcohol use (1.4% cirrhosis prevalence). It is clear that synergism of these risk factors plays a major role in development of clinically significant liver disease.

Similarly, body mass index was the most predictive measure of identifying cases of elevated liver stiffness. Using the inner city practice patients as a training population, in those with hazardous alcohol use 38% of TE scans could have been avoided with 90% sensitivity at a BMI threshold of 25kg/m^2 and in those with type 2 diabetes 29% of TE scans could have been avoided

at the same diagnostic sensitivity with a BMI threshold of 27.4 kg/m^2. However, these cutoffs need validation in independent samples for confirmation. Simple fibrosis biomarkers (validated particularly in secondary care to rule out advanced fibrosis in NAFLD) performed poorly for detection of elevated liver stiffness in both hazardous alcohol users and NAFLD risk patients. Currently these alternative investigations couldn't be recommended in primary care to reduce the number of TE scans adequately.

iv) To explore the patient perspectives of liver disease investigation of the pathway and get some preliminary insights into the uptake of subsequent lifestyle changes.

A qualitative substudy was conducted in which in-depth semi structured interviews were carried out with 20 patients who had undergone liver disease stratification in the community study between 6 months and 2 years prior. NAFLD in particular has been poorly studied in the qualitative literature; this study therefore gave novel insights into patients with type 2 diabetes and/or NAFLD including the facilitators and barriers to change, and their experience of community liver disease screening.

Overall the process of undergoing TE was linked to subsequent lifestyle change, both in terms of unexpected abnormal liver stiffness results, but in addition the process of screening increased patient awareness of their risk for liver disease. The majority of patients described initiating lifestyle changes following TE. Interestingly in patients with hazardous alcohol use even normal liver stiffness readings resulted in adjusted lifestyle. Changes were less likely to be initiated or sustained in type 2 diabetes, due to greater

barriers to change being reported e.g. further lifestyle changes were felt to be unfeasible (due to other comorbidities or changes already made at the time of diabetes diagnosis), lifestyle changes did not provide an instant fix, and patients still feeling describing themselves as healthy due to a lack of liver disease symptoms.

Overall, the community liver disease screening process was described as a positive experience by most participants. Positive experiences described included the convenience of having the TE performed in primary care, quick appointments and the non-invasive nature of the test. Negative comments of the TE scan itself were limited to mild discomfort in one patient and failed liver stiffness acquisition in another.

Implications

It is important to state that the research in this thesis has been on a relatively small primary care population (20,868 patients), therefore it is difficult to make strong recommendations on a national level from these pilot data alone. However, national liver disease strategy is already changing, and indeed the Lancet Liver Commission document highlights the need for new strategies in UK population for tackling liver disease and describes the current research as an exemplar of primary care based liver disease screening(22). As described in the introductory chapter to this thesis, screening criteria from Wilson and Jungner(138)and more recent guidance from the National Screening Committee(139)outline the necessary factors which should be met before national screening for a disease or health condition is initiated. The research in this thesis furthers the understanding of

pathways for screening for chronic liver disease in the United Kingdom, including the acceptability and validity of TE as the investigation to be used for this purpose, and identification of particular risk groups (type 2 diabetes, or those with multiple liver disease risk factors) whom should be screened. However, there remain a number of criteria for which there is either limited or absent data to support screening for chronic liver disease on a national scale. The following two sections therefore provide numerous recommendations for further work to confirm the optimal and most cost effective method of community liver disease screening prior to recommending an overall national strategy.

The largest number and percentage of liver disease diagnoses were found in those patients with type 2 diabetes as their risk factor (32% had elevated liver stiffness, and overall the studied type 2 diabetes population had a diagnosed cirrhosis prevalence of 2%). As already discussed, this is a similar prevalence to other primary and secondary care studies; although this research represents the only study in the UK of unselected patients with type 2 diabetes. This therefore is the group where strategy for liver disease screening needs to be most urgently addressed, with further regional or even national pilots using TE. Although lifestyle behavioural change appears difficult in this group, nonetheless identification of liver disease in these patients might be helpful in two main ways. Firstly, identification of patients with cirrhosis enables access to cirrhosis surveillance measures which have evidence base to reduce liver-related morbidity and mortality (endoscopy for varices surveillance and ultrasound and alpha fetoprotein measurement for

hepatocellular carcinoma). Secondly, elevated liver stiffness identifies a group at highest risk of adverse health outcomes who need more intensive diabetes monitoring and consideration of altered medical management, such as the introduction of pioglitazone or liraglutide which might improve both diabetes control and liver disease progression in NAFLD.

In patients with hazardous alcohol use, fewer new cases of chronic liver disease were identified compared to other risk factor groups and many of these patients had obesity or type 2 diabetes as additional liver disease risk factors. This may be in part due to poorer attendance for TE in this group. Nonetheless TE screening in such patients should still be considered. The TE scan appointment provides an opportunity to initiate lifestyle intervention such as Brief Interventions for alcohol, for which the numbers needed to treat to reduce alcohol consumption are approximately 10(132, 133). In addition the TE scan itself, whether normal or abnormal, appears to have an important behavioural effect both directly through the scan result and indirectly through knowledge gained during the screening procedure. It is possible that a strategy which incorporates repeat liver disease screening at an interval using TE will contribute to sustained or additional lifestyle changes. Alcohol reduction on a population scale will not only reduce liver-related deaths, but other morbidity due to cardiovascular disease and cancer, and also reduce healthcare utilisation costs.

Population alcohol consumption has stabilised in recent years partly due to public health interventions for alcohol being publicised in the media (including a very recent reduction in what is considered safe weekly alcohol

consumption limits). Obesity and type 2 diabetes have been subject to much less coverage, despite a clear synergism between alcohol use and these metabolic risk factors with regards to risk of liver disease and death. The qualitative research study highlights the lack of knowledge regarding obesity and type 2 diabetes in the population as risk factors for liver disease development. In addition to consideration of liver disease screening in these groups, public health campaigns highlighting the adverse health consequences of obesity and type 2 diabetes are of paramount importance. Moreover, education courses enhancing the knowledge of liver disease in patients with type 2 diabetes or obesity are urgently required.

Limitations and Recommendations for Future Work

Further to the reported conclusions from this body of work, there are a number of important areas in which additional studies are required to inform the most valid strategy for chronic liver disease stratification in primary care in the United Kingdom.

The current liver disease investigation algorithm was studied in a diverse primary care population with liver disease risk factors in keeping with known UK population estimates. Nonetheless, a total adult population of 20,868 patients represents a relatively small number to make generalised recommendations for national liver disease screening strategy. The logical next step would be to repeat the pilot study outside of Nottinghamshire primary care, and if possible using a larger patient population (for example, all general practices within a defined Clinical Commissioning Group). This would determine whether the current investigation pathway is functional in

both an independent healthcare region and when investigating greater patient numbers, or if alteration of the studied risk factors or structure of investigations and community clinic follow-up are required prior to implementation on a wider scale. One potential problem of implementing the pathway at a larger scale, for example, might be the difficulty of stratifying and subsequently reviewing in clinic a large number of patients with liver disease in a short defined time period. A possible alteration of the structure of the investigation pathway which could therefore be studied to enable screening of a larger patient population, could include training primary care nursing staff within a distinct Clinical Commissioning Group, rather than secondary care nurses, to perform TE. In addition, further study would also provide a validation population to confirm conclusions drawn from the current research, such as the ability for specific body mass index cutoffs to save a significant number of TE scans and the lifestyle behaviour changes suggested in the qualitative substudy.

The cost effectiveness of an investigation pathway is a key consideration for healthcare providers prior to alterations in service provision. Previous analyses by the University of York have suggested that in secondary care the utilisation of TE as an alternative to liver biopsy would be cost effective(131). Screening in primary care would represent a much larger population and therefore overall cost to healthcare. In the present research approximately 10% of patients in the participating general practices had defined risk factors for chronic liver disease; in the UK this would equate to approximately 7 million people who would require chronic liver disease

screening. The utilisation of TE on such a large scale would create upfront costs from new diagnoses and subsequent need for hospital follow-up. In contrast it is likely to result in long term cost savings by reducing the number of hospital admissions from decompensated cirrhosis due to earlier liver disease detection and subsequent lifestyle or medical intervention. Formal health economic modelling of this liver disease pathway is required to determine both its initial affordability and cost effectiveness on a regional and national scale. This would include comparison of the cost effectiveness of liver disease stratification using different pathway setups such as an initial screening step using non-invasive fibrosis biomarkers, comparison of different risk factor groups and comparison of socioeconomically distinct healthcare regions. Patient level data from the pilot studies performed to date might be utilised to inform the proportion of patients starting in specific healthcare states for formal Markov modelling of long term outcomes using the investigation pathway. Given the differences in liver disease diagnosis and longitudinal outcomes in patients with ALD and NAFLD, separate modelling for both health states would be required. Demonstration that the pathway is cost effective (if this were the case) would further the confidence in utilising it in a larger population and the comparative analyses described above would ultimately decide the best structure of the investigation in different healthcare regions.

In the current research, obesity and body mass index measurements were important predictors of which patients were diagnosed with clinically significant liver disease and cirrhosis. An important synergism between

obesity and both hazardous alcohol use and type 2 diabetes was demonstrated. As obesity wasn't studied as a standalone risk factor for liver disease, it is likely that those patients with a greater risk of liver disease due to additional risk factors (hazardous alcohol use, type 2 diabetes and/or abnormal ALT levels) have been investigated. However, the findings provide a strong argument for a further study to determine how much additional liver disease would be detected by screening all obese patients in a population. It is possible that yet more cases of cirrhosis would be detected with this less selective screening approach; however this needs to be balanced against the need to screen in excess of 25% of the primary care population. This highlights the need for a further pilot study addressing this question in a small primary care population. Importantly, the recent development of an XL probe which can be used with the portable Fibroscan FS402 system utilised in the current research means that a pathway which investigates obesity as a risk factor could now be purely performed in a primary care setting without the need for hospital XL scans.

In addition to accurate cross-sectional chronic liver disease stratification, several studies in secondary care have demonstrated that baseline liver stiffness measurements subsequently predict important liver-related outcomes. Perhaps the most robust and validated data, which have been adopted by recent guidance in the BAVENO VI consensus, is the high negative predictive value of liver stiffness measurements less than 21 kilopascals for developing portal hypertension in the following two years(141, 209). In a primary care setting the longitudinal prediction of adverse

outcomes using TE (including cirrhosis development, decompensation and death due to liver or cardiovascular disease) has not been studied. Patients in the current research have consented to longitudinal follow-up of their primary care data, which provide an opportunity to determine whether liver stiffness measurements are of both cross-sectional and prognostic benefit in primary care. Furthermore, the consented cohort also provides a population who might undergo future liver stiffness measurements at an interval (for example, 3-5 years later) which would help phenotype those patients who are at risk of progressive liver fibrosis. Clearly identifying those patients who are at greatest future risk accurately would be of the greatest benefit for determining subsequent medical intervention and secondary care follow-up.

A further limitation of the current research is that only a small percentage of patients with hazardous alcohol use as their risk factor for liver disease attended for liver disease screening. The relatively low number of liver disease diagnoses made in this group may be due to inadvertent screening of a mostly 'worried well' population with only mild to moderate increase in alcohol consumption. It is difficult to foresee an approach in primary care which increases attendance, however screening of patients in community-based drug and alcohol rehabilitation units should be considered. Previous European studies have demonstrated the feasibility of investigating using TE in such units(158, 277). Attendees to drug and alcohol units would also represent a group who could be screened opportunistically, and are more likely to represent a drinking population at greatest risk of liver fibrosis and cirrhosis development.

Conclusion

In summary, a new pathway investigating patients with liver disease risk factors using Transient Elastography (TE) was feasible to implement in a small UK primary care population. It resulted in a significantly increased number of cirrhosis diagnoses, the majority of which had type 2 diabetes or obesity as risk factors for chronic liver disease. The minimum cirrhosis prevalence in the type 2 diabetes group was 2%. Patient experience of investigation was positive, and the process of undergoing TE appeared to be an adjunct to lifestyle change by improving patients' awareness of health (both their risk factor for disease and new diagnosis of chronic liver disease) Body mass index measurements, rather than previously validated simple fibrosis markers, might be used to optimise the investigation pathway. However, further study to validate these findings in an independent and larger primary care population are recommended before implementation of screening using TE on a national scale.

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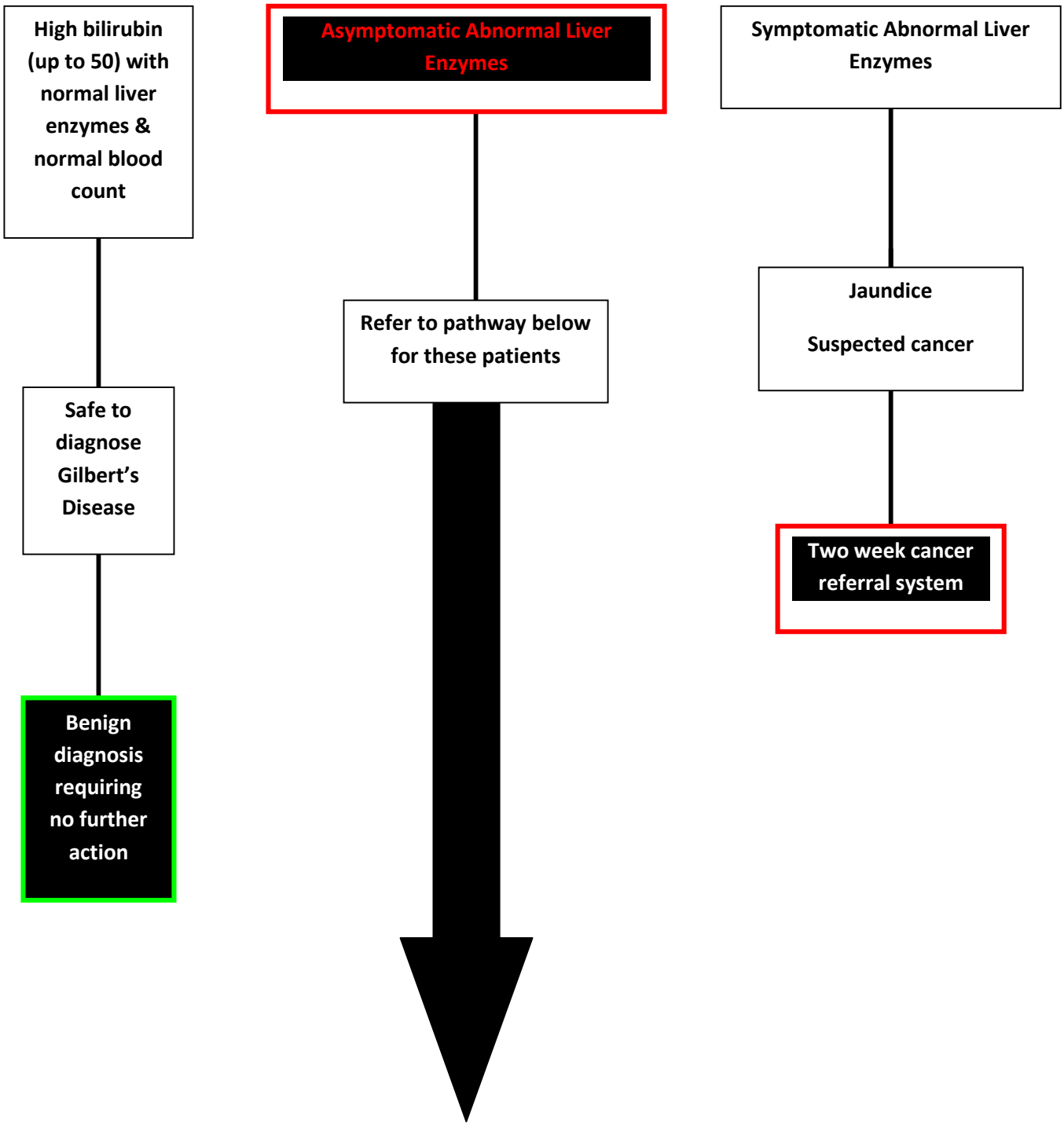
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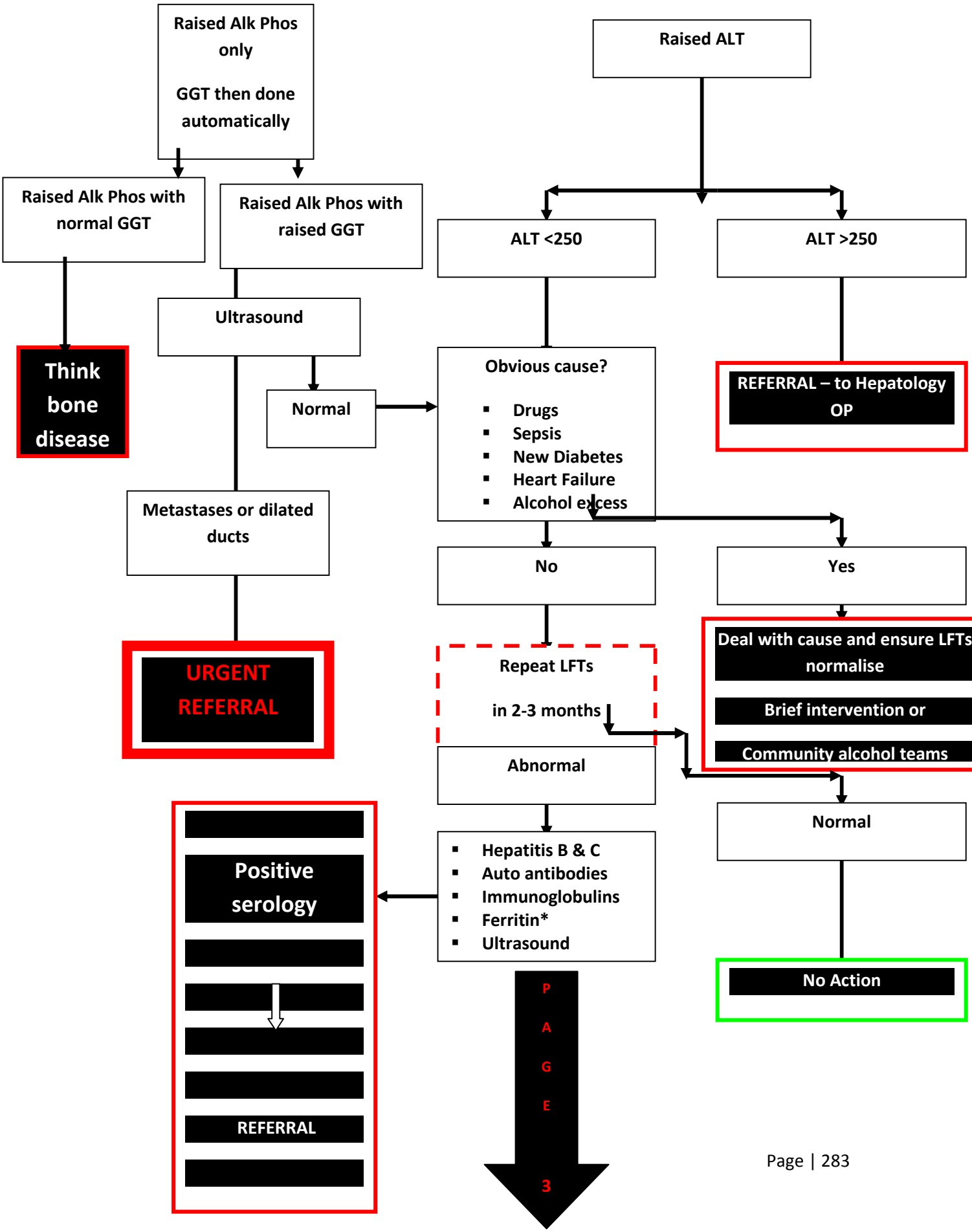
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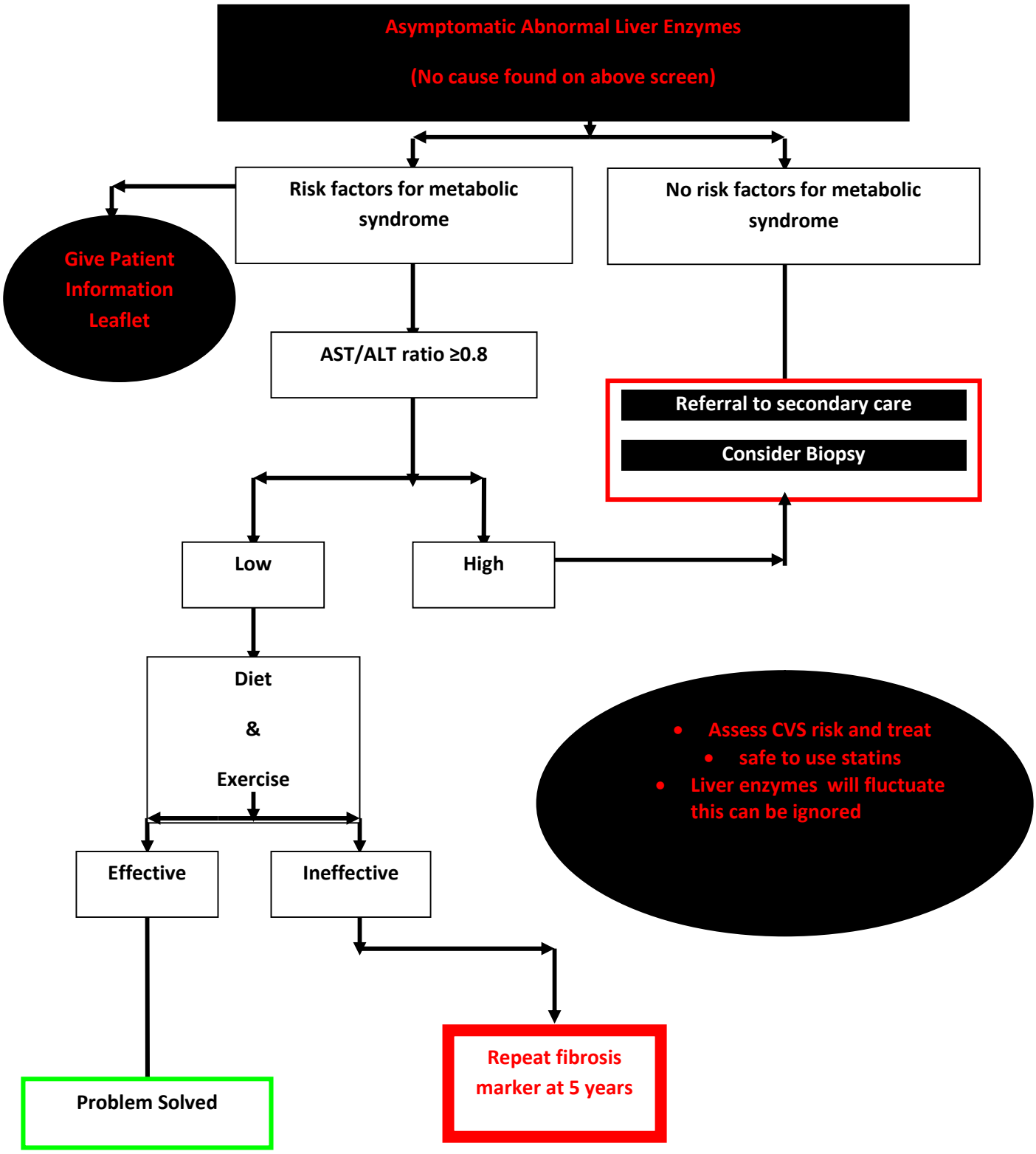
Appendices

Appendix A – Nottinghamshire Abnormal Liver Function Test Guidelines



Nottinghamshire Guidelines for Investigating Asymptomatic Abnormal Liver Enzymes




Asymptomatic Abnormal Liver Enzymes
(No cause found on above screen)
Risk factors for metabolic syndrome
No risk factors for metabolic syndrome
Give Patient Information Leaflet
AST/ALT ratio ≥0.8
Referral to secondary care
Consider Biopsy
Low
High
Diet
&
Exercise
Assess CVS risk and treat
safe to use statins
Liver enzymes will fluctuate this can be ignored
Effective
Ineffective
Problem Solved
Repeat fibrosis marker at 5 years

Appendix B. Search algorithms utilised for electronic databases (Medline, Embase and Web of Science) in the systematic review

Database: Ovid MEDLINE(R) <1946 to November Week 3 2014>
Search Strategy:
Results: **329 hits**

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1 exp Liver Cirrhosis/di [Diagnosis] (7647)
2 exp Fatty Liver/di [Diagnosis] (3112)
3 exp Liver Diseases, Alcoholic/di [Diagnosis] (1367)
4 (hepatic fibrosis or Chronic liver disease* or advanced fibrosis or non alcoholic fatty liver disease* or NAFLD or NAFL or alcoholic liver disease* or ALD or liver fibrosis* or hepatic cirrhos* or liver cirrhos* or fatty liver disease* or fatty liver or advanced fibrosis).mp. (113886)
5 exp Biological Markers/ (669858)
6 exp Elasticity Imaging Techniques/ (3985)
7 exp Diagnostic Imaging/ (1816061)
8 (non invasive biomarker* or non invasive biological marker* or non invasive marker* or fibroscan or liver stiffness or transient elastography or ultrasound abdomen or ARFI or liver function test* or LFT* or fibrotest* or fib4 or Lok or FORNS or APRI or ELF or NFS or BAAT or BARD or noninvasive biomarker* or noninvasive biological marker* or noninvasive marker* or elastogram* or sonoelastograph* or imaging tissue elastic or elasticity imaging technique*).mp. (42847)
9 exp Family Practice/ or exp General Practice/ (65915)
10 exp Primary Health Care/ (84294)
11 exp Community Health Services/ (514681)
12 (gp or general practice* or family practice* or primary care or communit* or outreach).mp. (539188)
13 1 or 2 or 3 (10904)
14 5 or 6 or 7 or 8 (2473667)
15 4 and 14 (23298)
16 13 and 14 (4877)
17 9 or 10 or 11 or 12 (962504)
18 15 or 16 (23432)
19 17 and 18 (329)

Database: Embase <1980 to 2015 Week 01>
Search Strategy:
Results: **274 hits**

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1 exp Liver Cirrhosis/di [Diagnosis] (10375)
2 exp Fatty Liver/di [Diagnosis] (4932)
3 exp Liver Diseases, Alcoholic/di [Diagnosis] (1672)
4 (hepatic fibrosis or Chronic liver disease* or advanced fibrosis or non alcoholic fatty liver disease* or NAFLD or
NAFL or alcoholic liver disease* or ALD or liver fibrosis* or hepatic cirrhos* or liver cirrhos* or fatty liver disease* or fatty liver or advanced fibrosis).mp. (172281)
5 exp Biological Markers/ (136914)
6 exp Elasticity Imaging Techniques/ (6192)
7 exp Diagnostic Imaging/ (120239)
8 (non invasive biomarker* or non invasive biological marker* or non invasive marker* or fibroscan or liver stiffness or transient elastography or ultrasound abdomen or ARFI or liver function test* or LFT* or fibrotest* or fib4 or LOk or

FORNS or APRI or ELF or NFS or BAAT or BARD or noninvasive biomarker* or noninvasive biological marker* or noninvasive marker* or elastogram* or sonoelastograph* or imaging tissue elastic or elasticity imaging technique*).mp. (55678)
9 exp Family Practice/ or exp General Practice/ (68233)
10 exp Primary Health Care/ (110827)
11 exp Community Health Services/ (99163)
12 (gp or general practice* or family practice* or primary care or communit* or outreach).mp. (663151)
13 exp chronic liver disease/di [Diagnosis] (1122)
14 exp early diagnosis/ (72202)
15 exp liver fibrosis/ (26007)
16 exp diagnosis/ (4570720)
17 exp non invasive measurement/ (13716)
18 chronic liver disease/ (12578)
19 exp liver cirrhosis/ (109545)
20 exp fatty liver/ (39198)
21 exp nonalcoholic fatty liver/ or exp alcohol liver disease/ (31283)
22 4 or 15 or 18 or 19 or 20 or 21 (185464)
23 5 or 6 or 7 or 8 or 14 or 17 (389042)
24 (22 or 1 or 2 or 3) and 23 (17179)
25 9 or 10 or 11 or 12 (722145)
26 24 and 25 (274)

Web of Science (169 hits)
Search performed 7th January 2015:
1 ((cirrhos* or (fatty liver) or (advanced fibrosis) or (non alcoholic fatty liver disease) or (hepatic fibrosis) or (liver fibrosis) or (chronic liver disease*) or NAFLD or NAFL or (alcoholic liver disease*) or ALD)) (175235)
2 ((non invasive biomarker*) or (non invasive biological marker*) or (non invasive marker*) or Fibroscan or (liver stiffness) or (transient elastography) or (ultrasound abdomen) or ARFI or (live function test*) or fibrotest* or fib4 or LOK or FORNS or APRI or ELF or NFS or BAAT or BARD or elastogram* or sonoelastograph* or (imaging tissue elastic*) or (elasticity imag*)) (56346)
3 2 and 1 (8577)
4 ((general practice*) or (family practice*) or gp or gps or communit* or (primary care) or (primary healthcare) or outreach) (1,008,641)
5 4 and 3 (169)

Appendix C: Read Code Search Strategy Used to Identify Patients With Type 2 Diabetes or Hazardous Alcohol Use

Type 2 Diabetes:

Read Code	And Children*?	Code	QOF Associated$^{\alpha}$?
Type 2 Diabetes	Yes	X40JS	Yes
Insulin Treated Type 2 Diabetes Mellitus	No	X40J6	Yes
Type 2 Diabetes on Insulin	No	XalfG	No
Type 2 Diabetes on Diet Only	No	XalfI	No

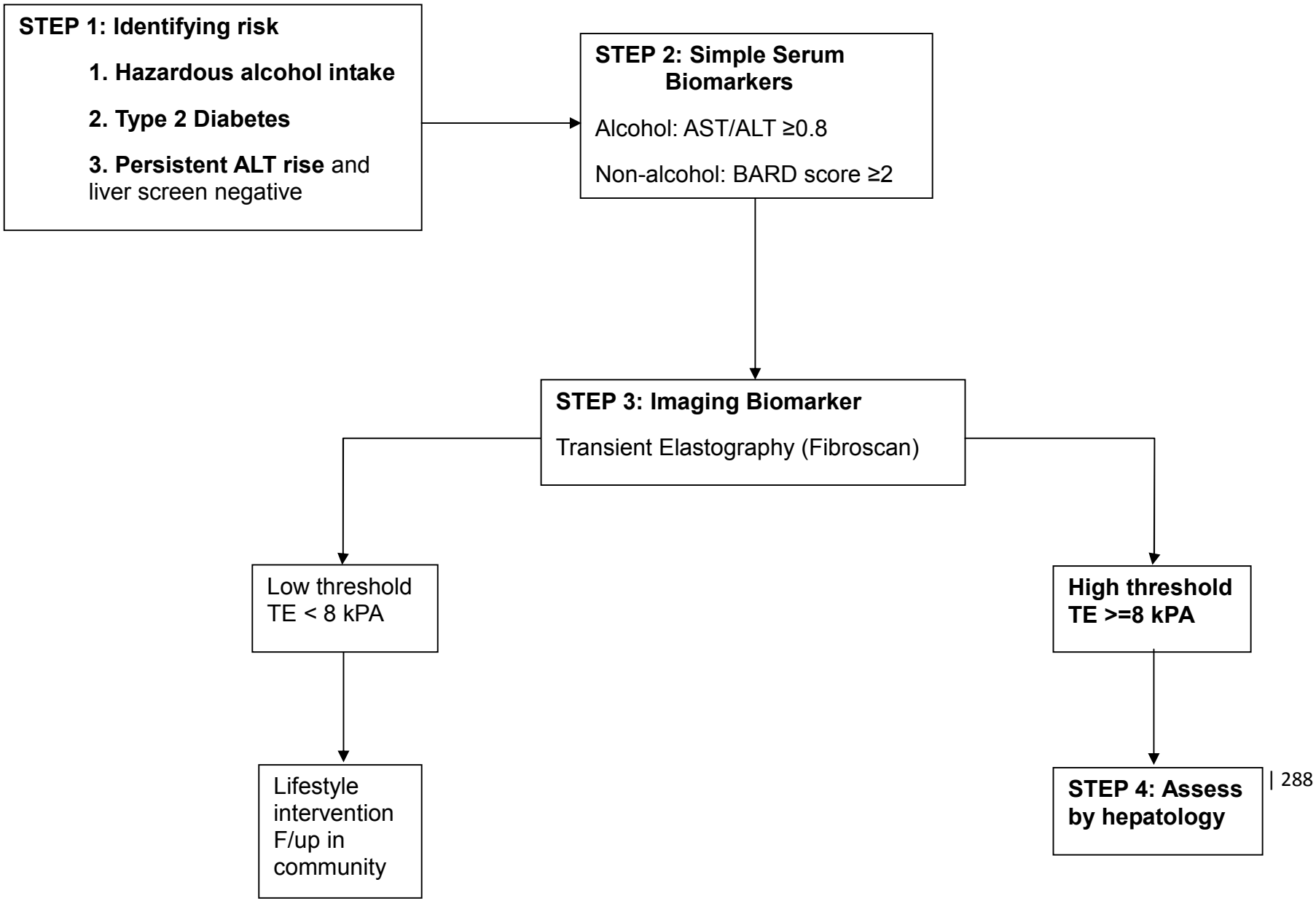
Hazardous Alcohol Use:

Read Code	And Children*?	Code	QOF Associated$^{\alpha}$?
Hazardous Alcohol Use	No	XaKVA	Yes
Harmful Alcohol Use	No	XaKVB	Yes
Problem Drinker	No	Ub01R	Yes
Higher Risk Drinking	No	XaXje	Yes
Chronic Alcoholism	Yes	XE1YQ	No
Alcohol Abuse	Yes	Xa1y2	No
Alcohol intake above recommended sensible limits	No	136K	No
Alcohol Dependence Syndrome NOS	No	E232	No

*SystmOne utilises Read Codes which are organised in categories and lower order sub-categories. A single Read Code may have several levels of sub-category which branch off of one another. The column 'and children' means that the searched Read Code had further sub-categories attached which were automatically included by the Read Code search algorithm.

α- QOF = Quality and Outcomes Framework, an annual reward and incentive programme utilised within the primary care.

Appendix D: Nottingham Community Study Investigation Pathway – Rushcliffe Phase



Appendix E: Nottingham Digestive Diseases Biomedical Research Unit (NDD BRU) Database Consent Form

Participant Identification No……..

Nottingham Digestive Diseases Database Study

	Please initial box
1. I confirm that I have read and understand the patient information sheet dated 26/01/2010 (version 1.2) for the above study and have had the opportunity to ask questions.	
2. I understand that my participation is voluntary and will not affect my medical care or legal rights in any way.	
3. I give permission for my medical notes and any data collected as part of my routine NHS care to be stored electronically as part of this study and be accessed and analysed by responsible individuals from the Nottingham Digestive Diseases Centre. (NDDC). I understand that any published information obtained from my participation in this study will not contain any personal information.	
4 I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.	
5. I understand and agree that parts of my medical information and data may be passed to other researchers outside of the NDDC team & organisations involved in the research on the understanding that my personal patient confidentiality will be maintained.	
6. I give permission to notify my GP or Hospital Doctor of any results which the researchers deem to be of clinical significance.	
7. I agree to be contacted in the future with information regarding future clinical trials relevant to my condition.	
8. I agree to take part in the above study.	

_____	__ _____	_____
Name of Patient	Date	Signature
_____	_____	_____
Name of Person taking consent	Date	Signature

Appendix F: Clinical and Laboratory Test Features of Patients Diagnosed With Cirrhosis

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, PHG = portal hypertensive gastropathy, T2DM = type 2 diabetes.

Appendix G: Search Algorithm used to Identify Patients with Cirrhosis from the SystmOne Primary Care Database

Read Code	And Children*?	Code	QOF$^{\alpha}$
Cirrhosis of liver	Yes	X307L	No
Oesophageal Varices	Yes	X2063	No
Ascites	Yes	Xa9C5	No

*SystmOne utilises Read Codes which are organised in categories and lower order sub-categories. A single Read Code may have several levels of sub-category which branch off of one another. The column 'and children' means that the searched Read Code had further sub-categories attached which were automatically included by the Read Code search algorithm.

α- QOF = Quality and Outcomes Framework, an annual reward and incentive programme utilised within the primary care.

In total, 43 patients were identified, the records of whom were hand searched to confirm evidence of cirrhosis. Subsequently, 20 cases were excluded for the following reasons:

Non-cirrhotic chronic liver disease (n=18)
- Alcoholic liver disease (n=9)
- Primary Biliary Cholangitis (n=6)
- Chronic Viral Hepatitis (n=2)
- Hereditary haemochromatosis (n=1)

Ascites due to congestive cardiac failure (n=1)

Biliary Atresia (n=1)

Appendix H: Nottingham Community Study Cohort Consent Form

(Full version 2.0: date 03/05/2014)

Title of Study: The Stratification of Liver Disease in the Community Using Fibrosis Biomarkers

REC ref: 13/EM/0123

Name of Researcher:

Name of Participant: **Please initial box**

1. I confirm that I have read and understand the information sheet version number 2.0 dated 03/05/2014 for the above study and have had the opportunity to ask questions. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, and without my medical care or legal rights being affected. I understand that should I withdraw then the information collected so far cannot be erased and that this information may still be used in the project analysis. ☐

3. I understand that relevant sections of my medical notes and data collected in the study may be looked at by authorised individuals from the University of Nottingham, the research group and regulatory authorities where it is relevant to my taking part in this study. I give permission for these individuals to have access to these records and to collect, store, analyse and publish information obtained from my participation in this study. I understand that my personal details will be kept confidential. ☐

4. I understand and agree that blood and urine samples may be taken for analysis of liver biomarkers ☐

5. I agree that blood and urine samples, excess to the current pathway, can be transferred to an authorised Biobank (such as the Nottingham Health Sciences Biobank). This will be used by researchers, including the current study team, to develop new tests and treatments. The samples or data used will be anonymised, and I will not be identified in anyway. ☐

6. I agree to future contact by the research team to discuss the impact of this pathway on my lifestyle. ☐

7. I understand that any interviews will be recorded and that anonymous direct quotes from the interview may be used in the study reports ☐

8. (Optional) I agree to future contact by the research team for relevant liver-related studies. ☐

9. I agree to my GP being informed of my participation in this study. ☐

10. I agree to the research team being allowed to contact the Medical Research Information Service (MRIS) database or my GP in order to retrieve information of my future illnesses and death, where this information is relevant to the current research study. ☐

11. I agree to take part in the above study. ☐

_____	_____	_____
Name of Participant	Date	Signature
_____	_____	_____
Name of Person taking consent (if different from Principal Investigator)	Date	Signature
_____	_____	_____
Name of Principal Investigator	Date	Signature

Appendix I: Nottingham Community Study Cohort Patient Information Sheet (Full Version 2.0 03/05/2014)

The Stratification of Liver Disease in the Community Using Fibrosis Biomarkers

You are being invited to take part in a research study. Before you decide, you need to understand why the research is being done and what it will involve for you. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

Background:

Significant liver disease continues to increase in the United Kingdom, with a rise in both advanced liver scarring (cirrhosis) and death due to liver disease in recent decades. Most causes of liver disease are preventable and reversible e.g. hazardous alcohol use, diabetes, obesity and intravenous drug use. Current strategies for discovering liver disease, using liver function blood tests, are inaccurate; therefore many patients with significant liver scarring have normal blood tests, and are only identified after the liver scarring becomes irreversible. It is of vital importance to identify the true levels and severity of liver disease in the community, how this impacts on future health, and find strategies to alter the population's lifestyle to reverse this worrying rise in liver disease.

We have preliminary data from pilot work in Nottinghamshire that a significant number of patients in the community might have undiagnosed, but significant, liver scarring. The community based strategy identifies many people with early and preventable liver scarring.

What is the purpose of the study?

We will study a large group of patients with risk for factors for liver disease, who underwent investigation in the community liver disease pilot. We aim to establish how the presence or absence of liver scarring affects a patient's future risk of liver and heart disease by monitoring future health records. We also aim to assess what factors lead to patients instigating lifestyle changes, when made aware of their risk of future liver disease.

Why have I been chosen?

Your GP practice took part in the community liver pilot, and you were identified as having a risk factor for the development of liver disease. As part of the liver pilot, you underwent a blood test and/or liver stiffness scan (Fibroscan). We are inviting all participants from the community liver pilot to take part in this research study.

Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form.

If you decide to take part you are still free to withdraw consent at any time, without giving a reason and can do this simply by informing the researcher whose contact details are at the end of this leaflet.

A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive or your legal rights.

What will happen to me if I take part?

If you are happy to take part in this study, an appointment will be made at the Nottingham Digestive Diseases Biomedical Research Unit in order to sign the consent form**.** In addition we ask to collect approximately 15ml of blood (half an egg cupful) and a 50ml urine sample. The appointment would last about 10 minutes in total.

We are interested in exploring the extent to which the liver scan has an impact on patient's health-related lifestyle choices. We would like to interview patients to discuss this in more depth. Interviews would be carried out by a trained nurse or researcher, and would last approximately one hour. Interviews would occur either face-to-face or on the telephone – face-to-face interviews could take place at the Nottingham Digestive Diseases Biomedical Research Unit, or the patient's home, depending on their preference. All interviews would be voice-recorded to allow analysis of the information provided. Any information given during the interview would remain confidential, and would affect neither the participant's legal rights nor standards of healthcare.

Over the coming years, the research team at The University of Nottingham would like to look at any patterns of ill health among people that have taken part in this research study. In particular we would like to study patterns of hospital admissions or risk of developing particular diseases, including heart disease and liver cirrhosis. This information would also notify us in the event of your death. In order to do this we would need to have access to your health records after this research project has ended. The Medical Research Information Service (MRIS) and General Register Office record this information. We would like your permission to pass details of your name, address and date of birth to these organisations in order for them to be able to supply us with the information we require.

What will happen if I don't want to carry on with the study?

You are free to withdraw from the study at any time without having to give a reason. If you withdraw from the study, we will destroy all your identifiable samples but the information collected so far cannot be erased and this information may still be used in the project analysis.

What are the possible disadvantages and risks of taking part?

Taking blood samples can cause temporary discomfort and temporary bruising. Otherwise, as the study essentially involves collection of current and future health-

related information, we anticipate no other risks from agreeing to take part in this study.

What are the possible benefits of taking part?

There is no immediate benefit to you from taking part in the research. However the information we get from this study may help us in three ways:

- We hope to identify specific factors for the future risk of both preventable liver and heart disease.

- We hope to improve the ways we investigate and treat liver disease, including advice given by healthcare professionals and what triggers important lifestyle changes in patients with a risk of future disease.

- We hope to use the information gained from this research to plan future trials of both medications and targeted lifestyle measures for patients at risk of future liver and heart disease. We will contact participants to invite them to take part in these future studies if they are of any relevance.

Participant payments

Participants will not be paid to participate in the study. Travel expenses will be offered for any hospital visits in excess of usual care.

What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions. The researchers contact details are given at the end of this information sheet. If you remain unhappy and wish to complain formally, the normal National Health Service complaints procedure or NHS Patient Advice & Liaison Service (PALS) office is available to you and can be contacted on Free phone: 0800 183 0204 or via the helpdesk, Main entrance Queens Medical Centre.

Will my taking part in this study be kept confidential?

We will follow ethical and legal practice and all information about you will be handled in confidence.

If you join the study, some parts of your medical records and the data collected for the study will be looked at by authorised persons from the University of Nottingham who are organising the research. They may also be looked at by authorised people to check that the study is being carried out correctly. All will have a duty of confidentiality to you as a research participant and we will do our best to meet this duty.

All information which is collected about you during the course of the research will be kept **strictly confidential**, stored in a secure and locked office, and on a password protected database. Any information about you which leaves the hospital will have

your name and address removed (anonymised) and a unique code will be used so that you cannot be recognised from it.

Your personal data (address, telephone number) will be kept for 12 months after the end of the study so that we are able to contact you about the findings of the study and possible follow-up studies (unless you advise us that you do not wish to be contacted). All other data (research data) will be kept securely for 7 years, or until the end of the study period (whichever occurs last). After this time your data will be disposed of securely. During this time all precautions will be taken by all those involved to maintain your confidentiality, only members of the research team will have access to your personal data

Involvement of the General Practitioner/Family Doctor (GP)

With your permission we will notify your GP of your participation in the trial.

What will happen to any samples I give?

As described above, in some patients we will collect approximately 15 mls of blood.

The blood samples you provide will be used for research tests that may diagnose liver scarring more accurately. With your permission, we would also like to store some of these samples for other future studies (this is indicated on your consent form). The samples will be stored with a code unique to you and securely at the Nottingham University Hospitals Biobank.

Some of these future studies may be carried out by researchers other than current team of Dr Guha, who ran the first study, including researchers working for commercial companies. Any samples or data used will be anonymised, and you will not be identified in anyway. If you do not agree to this any remaining samples will be disposed of in accordance with the Human Tissue Authority's codes of practice.

What will happen to the results of the research study?

We anticipate that the results of the study will be published in a scientific journal and will be presented at scientific meetings. The results will also be included in a Philosophy Doctorate (PhD) thesis. We will also produce a summary of the research on our website. A written summary of the research results can also be provided to study participants if requested. This may not occur until sometime after the research has finished. You and your details will remain strictly confidential and you will not personally be identified in any report or publication.

Who is organising and funding the research?

This study is being organised by The University of Nottingham and funded by the National Institute for Health Research Nottingham Digestive Diseases Centre (NIHR NDDC).

Who has reviewed the study?

All research in the NHS is looked at by an independent group of people called a Research Ethics Committee to protect your safety, rights well being and dignity. This study has been reviewed and given favourable opinion by the Leicester Research Ethics Committee.

Who do I contact for further information on this study?

Dr Neil Guha (Chief Investigator)
NDDC Biomedical Research Unit
E Floor, West Block, QMC
Nottingham
NG7 2UH.
Telephone: 0115 9249924 ext. 64415
Email: Neil.Guha@nuh.nhs.uk

Dr David Harman (Research Fellow)
NDDC Biomedical Research Unit
E Floor, West Block, QMC
Nottingham
NG7 2UH
0115 9249924 ext.70610
Email:
david.harman@nottingham.ac.uk

Thank you for reading this information sheet.

Appendix J: Provisional Interview Schedule

(Version 2.0 03/05/2014)

Study title: The Stratification of Liver Disease in the Community Using Fibrosis Biomarkers

Introduction and thanks

Confirm participant agrees with the use of the digital recorder. Reassure them data will be treated confidentially, and that if any quotes are used in study reports, they will not identify them in any way. Confirm consent to take part; assure that they are free to withdraw at any time.

Background to liver scan (including prior knowledge/health beliefs)

Ask about name/age/demographics.

Prior knowledge of liver disease/views of health:

- Before being contacted about the liver tests, how would you describe your health?
- Can you tell me what you knew about the risks of excessive alcohol consumption/diabetes? (probe to ask about liver disease if not mentioned by participant)
- Ask about patient's own risk – alcohol consumption/diabetes control pre-scan?
- Had you intended to make any attempts to improve your lifestyle/health prior to the liver tests? (probe to ask why/why no prior attempts). If so, what did you do? What triggered the previous lifestyle changes?
- Who contacted you about having tests to check your liver function?
- What information did you receive about the scan before having it?
- Did you understand why you were contacted to have the scan done?
- How did you feel about being contacted?

Experiences of liver scan

Scan experience and results:

- When did you have the liver scan done?

- Please take me through what you remember about having the liver scan done?
- How would you describe your feelings about having this test done?
- Did you understand what the scan was looking for?
- Can you tell me about your results from the liver scan? Probe around who discussed the results and were they explained clearly?
- Have you remembered the number result (liver stiffness) that the scan produced? If so, did this result mean anything to you?
- How did the scan results make you feel at the time?

Subsequent health behaviours:

- Was there anything you did differently after the test? If yes, please describe more for me? If no changes made, what were the reasons for this?
- Can you talk me through the lifestyle changes that you have made? Individual probes about alcohol/exercise/diet as appropriate
- How did you find making these changes?
- What were your main reasons for making these changes?
- Have you managed to maintain these changes? (probe to ask about additional support/advice required)
- If so – how have you found maintaining these lifestyle changes over a longer period? Has anything been particularly challenging? Has anything helped to make changes?
- If not - what did you find difficult about continuing these lifestyle changes?

Current Health Beliefs

- Did having the liver tests have an impact on how you view your health?
- Since having the tests, is there anything you have learned about liver disease?
- To what extent have your health beliefs changed since having the liver scan?
- To what extent has information from the doctors or nurses had a role in changing how you view your health?
- (if no lifestyle change) What would prompt you to make lifestyle changes?

Future follow-up

- How important would having repeat tests be for you? Probe why/why not important.

Closing the Interview

- Is there anything else you would like to say about your experience of the liver tests?
- Thanks and interview closure.

General probes/prompt:

Could you tell me a bit more about that?
What do you mean by….
What could have been done differently?
How did you find that experience?
How did that make you feel?
(adjectives) – why/what was it you found e.g. scary…

Appendix K: Coding list following initial analysis of 20 semi-structured interviews

Code Name	Code Number	First Used (Interview/ Line number)
Recognition that drinking a lot of alcohol	001	TJ001, 19
Lack of interest in world due to alcohol	002	TJ001, 25-26
Medical advice about excessive alcohol	003	TJ001, 29-30
Previously abnormal liver blood tests	004	TJ001, 30-31
Alcohol causing other health issues	005	TJ001, 36-37
Initiating lifestyle change for family	006	TJ001, 48
Alcohol reduction to feel like self again (incl. symptoms)	007	TJ001, 49
Search for knowledge pre-liver scan	008	TJ001, 58-59 and 61-62
Happy to be contacted for scan	009	TJ001, 74
Prior knowledge – alcohol bad for liver	010	TJ001, 77-78
Shock/surprise at abnormal scan result/diagnosis	011	TJ001, 81-82
Reassurance from nursing team	012	TJ001, 82-83
Prior knowledge – meaning of scan result	013	TJ001, 93-94
Abnormal liver scan triggering lifestyle change	014	TJ001, 96-97
Having liver scan 'to do something about drinking'	015	TJ001, 100-101
Convenience of scan at GP location	016	TJ001, 132
Alcohol abstinence easier than lifestyle change	017	TJ001, 145-147
Craving food – barrier to lifestyle change	018	TJ001, 150-151

Attempted lifestyle change	019	TJ001, 151-152
Homeopathy as adjunct to lifestyle change	020	TJ001, 158-159
Fear of death – reduction in alcohol	021	TJ001, 166
Family problems as trigger to alcohol drinking	022	TJ001, 168-171
Experience of liver disease symptoms in others – barrier to drinking	023	TJ001, 173-175
Gain freedom from stopping alcohol	024	TJ001, 190-192
Gradual process of abstinence	025	TJ001, 196-197
Alcohol abstinence easy	026	TJ001, 199-201
Diet change biggest challenge	027	TJ001, 211-212
Keep something in your life (vice)	028	TJ001, 217-219
Knowledge of health due to family illness	029	TJ001, 221-223
Having liver tests confirming prior health knowledge	030	TJ001, 229
Worry of liver disease progression	031	TJ001, 230-231
Medical team accessible for support	032	TJ001, 236-238
Lifestyle changes reinforced by change in liver test results	033	TJ001, 240-251
Repeating liver tests to reduce anxiety	034	TJ001, 254
Support to break cycle of drinking	035	TJ001, 286-287
Scared of having cirrhosis diagnosis	036	TJ001, 301-302
Lifestyle change an ‘active’ decision	037	TJ001, 307-308
Alcohol drinking as self-medication	038	TJ001, 330-332
Repeated GP Visits	039	MOC002, 21
GP inactivity despite abnormal liver blood tests	040	MOC002, 27
Prior knowledge – unaware diabetes is risk for liver disease	041	MOC002, 38-39

Worsening diabetes control pre-scan	042	MOC002, 43-44
Exercise limited – pain (barrier); co-morbidity	043	MOC002, 49-50
Diabetes raised awareness of food contents/diet	044	MOC002, 57-59
Feeling alone due to liver diagnosis	045	MOC002, 68-69
Meeting others with same disease helped coping	046	MOC002, 69-71
Depressed by liver diagnosis	047	MOC002, 71-73
Liver diagnosis explanation 'went over her head'	048	MOC002, 73-75
Difficult to accept diabetes led to liver disease	049	MOC002, 80-82
Lack of liver symptoms	050	MOC002, 82-83
Lifestyle change – prevent liver getting worse	051	MOC002, 91-92
Information well explained by nurses	052	MOC002, 105-106
Limited recall of liver tests	053	MOC002, 108-109
Had tests as keen to detect if something wrong	054	MOC002, 115-116
Mixed experience of liver biopsy	055	MOC002, 156-159
Explanation/understanding helped come to terms with diagnosis	056	MOC002, 170-171
Worried was going to die from liver cirrhosis	057	MOC002, 173-174
Sustained lifestyle change achieved	058	MOC002, 182-183
Intention to restart exercise	059	MOC002, 192-193
Gained weight despite lifestyle change	060	MOC002, 200-202
Diabetes triggered alcohol abstinence	061	MOC002, 210-212
Lifestyle change triggered by diabetes	062	MOC002, 218-219
Feels no further lifestyle change	063	MOC002, 244

possible		
Improved knowledge of liver since tests	064	MOC002, 249-250
Community appointments quicker than hospital	065	MOC002, 274-275
Community scan facilitated further tests	066	MOC002, 276-278
Happy for ongoing liver disease follow-up	067	MOC002, 285-287
Liver cirrhosis – death sentence	068	MOC002, 309-310
Liver diagnosis unfair/'why me'	069	MOC002, 318-320
Liver diagnosis unexpected	070	MOC002, 336-338
Limited recall of information regarding liver diagnosis	071	MOC002, 336-338
Unsure who to ask questions to	072	MOC002, 341-344
GP not used for support – lack of knowledge	073	MOC002, 363-365
Reduced mobility due to comorbidity (same as 43?)	074	WF003, 18-20
Attributing liver damage to diabetes	075	WF003, 25-27
Tries to be active despite co-morbidity	076	WF003, 51-52
Previous attempts at lifestyle change	077	WF003, 87
Medical advice about losing weight	078	WF003, 91-92
Concurrent lifestyle change in family – aiding lifestyle change	079	WF003, 102-104
Adequate information given prior to scan	080	WF003, 125-126
Expectation that wouldn't have significant liver problem	081	WF003, 174-175
Short term anxiety from diagnosis	082	WF003, 189-191
Contemplation of lifestyle change	083	WF003, 205-206

Keeping busy to reduce appetite	084	WF003, 233-235
Holiday/leisure as trigger to lifestyle change	085	WF003, 241-242
Difficult to sustain lifestyle change	086	WF003, 242-243
Liver disease diagnosis triggering lifestyle change	087	WF003, 257
Liver disease only due to alcohol	088	WF003, 276-277
Having liver tests to 'identify potential problem early'	089	WF003, 280-282
Abnormal liver test making patient feel health is important	090	WF003, 282-283
Repeat tests – uncertainty of liver disease progression	091	WF003, 296-299
Worsening/deterioration of liver disease as trigger to lifestyle change	092	WF003, 320-322
Lifestyle change would not have occurred without liver tests	093	WF003, 325-327
Describes self as healthy despite co-morbidity	094	JD006, 17
Falls – reduced confidence in mobility	095	JD006, 27-29
Poor diabetes control – medical view of target	096	JD006, 35-36
Complications of diabetes – 'nasty'	097	JD006, 44-45
Prior knowledge – complications of diabetes	098	JD006, 47-48
Feels diet change not difficult	099	JD006, 69-71
Gained weight due to co-morbidity	100	JD006, 77-78
Failed scan at GP	101	JD006, 86-87
Thought scan was part of research study	102	JD006, 90-91
Limited information given pre-scan	103	JD006, 94-95
Didn't consider at risk of liver disease	104	JD006, 99-100

as no alcohol		
Shock as no previous diabetes problems	105	JD006, 111-112
Scan uncomfortable/pressed hard on ribs	106	JD006, 120-121
Unsure what scan was looking for	107	JD006, 137-138
Family or friend history of alcohol/liver (awareness/wake-up call)	108	JD006, 145-146
Liver cirrhosis just an alcoholic problem	109	JD006, 144-145
Classes family member as alcoholic	110	JD006, 148-150
Nurse feedback r.e. abnormal result	111	JD006, 169-170
Unable to take all information in	112	JD006, 182-184
Need factsheet with liver diagnosis	113	JD006, 187-188
Liver biopsy – painful experience	114	JD006, 200-201
Difficult to cope with multiple ailments/new diagnosis	115	JD006, 208-210
Aim for improved diabetes control post diagnosis	116	JD006, 216-217
Friend died of diabetes/poor lifestyle	117	JD006, 235-238
Lifestyle views shaped by family diabetes experience	118	JD006, 239-240
Liver diagnosis increased will to improve lifestyle	119	JD006, 259-260
Liver diagnosis/scan increased/not increased awareness of own health	120	JD006, 276-278
Availability of someone to 'listen' important	121	JD006, 290-291
Good communication with liver team	122	JD006, 298-299
No prior complications of diabetes	123	RS004, 32-33
No symptoms from diabetes	124	RS004, 35-36

Experience of friend with diabetes	125	RS004, 38-39
Prior knowledge of liver disease symptoms	126	RS004, 57-58
Forgets to take diabetes medication – impact on diabetes control	127	RS004, 67-69
Unsure of what medications are for	128	RS004, 81
Active lifestyle before scan	129	RS004, 96-98
Family support at appointments	130	RS004, 97-99
Diet adherence variable	131	RS004, 101-103
Feels overweight	132	RS004, 110-112
Gained weight due to age/barrier to weight loss	133	RS004, 119-120
Nurse-led care/support for diabetes	134	RS004, 135-136
Expectation liver scan would be painful	135	RS004, 148-149
Scan painless/gentle	136	RS004, 158-159
Liver scan quick	137	RS004, 178-180
Discordance between scan result and recall	138	RS004, 196-197
Alcohol as cause of type 2 diabetes	139	RS004, 212-214
Previous harmful use of alcohol	140	RS004, 218-219
Previous alcohol intake would have caused damage if not stopped	141	RS004, 222-223
Relief that no major problem found	142	RS004, 233-234
Uncertainty of future diabetes complications	143	RS004, 243-245
Liver result ‘giving the all clear’	144	RS004, 250
Deliberately omitting medications – don’t need them	145	RS004, 310-312
No change to how views health post-scan	146	RS004, 315-316
Regular blood tests as diabetes follow	147	RS004, 341-342

up		
Danger to health would prompt further lifestyle change	148	RS004, 346
Would make lifestyle change if severe liver disease/health issue	149	RS004, 379-382
Would have further liver scan	150	RS004, 408-409
Gained weight after normal liver scan	151	RR005, 26-27
Contemplation of lifestyle change – to stop medication	152	RR005, 29-31
Does everything they want despite mobility issue	153	RR005, 51-52
Lifestyle change due to major health issue	154	RR005, 67-68
Education course for diabetes – increased knowledge	155	RR005, 71-72
Gotten away with previous hazardous lifestyle choices	156	RR005, 76-77
Invite for scan from GP	157	RR005, 109-110
Starting diabetes medication – 'admitting defeat'	158	RR005, 113-115
Co-morbidity – raised awareness of health	159	RR005, 121-122
GP service didn't work as scan failure	160	RR005, 149-153
Remembered numerical scan value	161	RR005, 179
Scan result given by GP	162	RR005, 200-201
Numerical values better for results communication – relate more	163	RR005, 209-213
Normal scan 'one less thing to worry about'/relief (?reduced future risk)	164	RR005, 241-242
No lifestyle change as normal liver result	165	RR005, 267-268
Advice from medical team important	166	RR005, 316-317

Nursing background	167	BK007, 6
Weight loss achieved pre-scan	168	BK007, 20
Unsure r.e. trigger to weight loss	169	BK007, 22-23
Gradual weight gain since retirement	170	BK007,28
Diet change attempted previously	171	BK007, 33-34
Support from chemist – weigh ins	172	BK007, 34-36
Education course r.e. diet/exercise	173	BK007, 38-40
Prior knowledge of health and liver (nursing)	174	BK007, 43-44
Lives alone – barrier to lifestyle change (motivation)	175	BK007, 49-51
Knowledge – NAFLD due to fat in diet	176	BK007, 57-58
No knowledge of obesity	177	BK007, 64
Previous diagnosis of fatty liver	178	BK007, 75-77
No anxiety from scan referral	179	BK007, 98-100
Result communication ‘didn’t mean a lot to patient’	180	BK007, 136-137
Didn’t remember numerical scan result	181	BK007, 139-140
Liver diagnosis not a worry as ‘fit and healthy’	182	BK007, 145
Liver biopsy not painful	183	BK007, 174
Age as trigger to lifestyle change	184	BK007, 221-222
Scan reinforced knowledge of alcohol/liver	185	BK007, 251-252
Scan experience of friend with hazardous alcohol	186	BK007, 269
No lifestyle change despite abnormal scan	187	BK007, 275-276
Portion control is a challenge	188	AH008, 58-59
Stable weight	189	AH008, 61-62

Complications of diabetes 'an eventuality	190	AH008, 134-135
Experience of 'well' diabetes in family	191	AH008, 137-139
Normal scan still triggered alcohol reduction	192	AH008, 153-154
Diet/exercise not changed after normal scan	193	AH008, 168
Routine to help maintain lifestyle changes	194	AH008, 184-185
Social life – trigger to drinking alcohol	195	AH008, 197
Repeat liver tests to allow lifestyle adjustment	196	AH008, 237-239
Subjectively good diabetes control	197	CB009, 42-43
No prior knowledge of liver disease causes	198	CB009, 49-50
Weight loss since liver diagnosis	199	CB009, 56-58
Increased exercise post scan	200	CB009, 60-62
Weight loss attributed to course/support	201	CB009, 73-74
Change in diet achieved post-scan	202	CB009, 74-78
Personalised programme devised for him	203	CB009, 88-90
Courses support lifestyle change/motivation	204	CB009, 88-90
Lifestyle information/education from scanning nurses	205	CB009, 127-129
Not worried as scan only slightly high	206	CB009, 138-139
Understanding that fat in the liver abnormal	207	CB009, 185-186
Education course 'suits him'/personalized	208	CB009, 203-205
Motivation of other's experiences at course	209	CB009, 208-211

Maintaining motivation to exercise hard when you are overweight	210	CB009, 225-227
Lifestyle change ‘not an instant fix’	211	CB009, 235-238
Alcohol intake stable pre- and post-scan	212	CB009, 281-283
Lifestyle changes should be simple, not dramatic	213	CB009, 340-342
Lifestyle change ‘must be something you like doing’	214	CB009, 348-350
Achieve regular exercise	215	PS010, 16-17
Reduced alcohol due to experiences of liver disease in others	216	PS010, 65-67
Wanted scan due to experiences of liver disease in others	217	PS010, 96-98
Nurses made feel at ease	218	PS010, 103-105
Would not prefer numerical scan results	219	PS010, 130-132
Lifestyle change in family also triggered by scan	220	PS010, 145-148
Reduction in alcohol as ‘precaution’	221	PS010, 151-152
Subjective healthy diet prior to scan	222	PS010, 159-162
No new liver knowledge after scan	223	PS010, 178
Medical advice had impact on reducing alcohol	224	PS010, 189-192
Repeat scan to ensure no new problems developed	225	PS010, 201-203
Having repeat scan to save NHS money	226	PS010, 225-227
Felt healthy prior to scan	227	LF011, 16-17
Gradual increase in alcohol intake	228	LF011, 26-27
Previous support from alcohol services didn’t help	229	LF011, 34-35

Didn't reduce alcohol previously – not concerned about health	230	LF011, 39-42
Possible liver cancer	231	LF011, 122-125
Surveillance for liver cancer	232	LF011, 141-143
Liver diagnosis a shock as no symptoms	233	LF011, 159-160
Difficult to reduce alcohol – lack of sleep	234	LF011, 188-191
Alcohol intake rising again as repeat scan 'ok'	235	LF011, 196-198
Drinking due to habit	236	LF011, 242
Increased drinking due to friendship group	237	LF011, 246
Gained weight due to change in diet	238	IS012, 35
Awareness of alcohol and risk to health	239	IS012, 66-67
Good recall of liver tests	240	IS012, 122-125
Habit/previous behaviour as barrier to lifestyle change	241	IS012, 185-188
Occasional binge drinking	242	IS012, 206-208
Limited information available about liver disease	243	IS012, 243-245
Poor diabetes control – lack of lifestyle change	244	JB013, 19-20
Not listened to medical advice about lifestyle	245	JB013, 22-23
Sedentary lifestyle	246	JB013, 46-47
Prior knowledge – link of diabetes and obesity	247	JB013, 67-69
Unaware of risks of liver biopsy pre-procedure	248	JB013, 121-125
Limited dietary change achieved	249	JB013, 151-153
Work as barrier to lifestyle change	250	JB013, 176-180

Access to gym – barrier to lifestyle change	251	JB013, 187-189
Liver diagnosis not seen as 'major' problem	252	JB013, 199-200
Lack of education r.e. weight as a health problem	253	JB013, 223-225
Symptoms/complications from diabetes	254	BH016, 12-15
Made ill by diabetes medications/side effects	255	BH016, 25-31
Lack of symptoms despite poor diabetes control	256	BH016, 40-43
Health ok as no symptoms	257	BH016, 64-67
Weight loss due to busy job	258	BH016, 74-77
Lost weight due to depression	259	BH016, 78-79
Lifestyle change not for health reasons	260	BH016, 91-92
Liver problems 'not talked about by people'	261	BH016, 154-155
Having liver scan to 'help others in future'	262	BH016, 191-194
Having liver scan to keep check on previous liver problems	263	BH016, 201-202
Didn't understand numerical liver stiffness result – no context	264	BH016, 262-265
Liver scans to reduce deaths in population	265	BH016, 320-323
Co-morbidity as barrier to healthy living	266	BH016, 350-352
Mental health as barrier to exercise	267	BH016, 408-410
Use of alcohol support services	268	MS015, 46-47
Stress as trigger to alcohol use	269	MS015, 69-70
Surprise that liver scan normal given risk factor	270	MS015, 129-131
Worried about symptoms from alcohol	271	MS015, 181-184

misuse		
Aiming for controlled drinking	272	MS015, 240-242
Different strength alcohol – patient perceived risk of liver disease	273	MS015, 286-289
Prior knowledge – liver regeneration	274	JH014, 105-106
Doesn't feel need to change diet	275	JH014, 222-224
Knowledge of liver regeneration reduced anxiety of diagnosis	276	JH014, 266-268
Mixed messages – advice on alcohol reduction	277	JH014, 279-280
Shock at poor diabetes control – no symptoms	278	JD017, 32-34
Knowledge/reading as trigger to lifestyle change	279	JD017, 80-82
Understood numerical liver stiffness reading as context given	280	JD017, 163-166
Symptoms as trigger to lifestyle change	281	JD017, 223-225
Lack of education –barrier to lifestyle change	282	JD017, 233-235
'Night work'/gaining sleep as trigger to alcohol drinking	283	RW018, 40-42
'Catching up' on previous lack of alcohol excess	285	RW018, 62-63
Shocked by risk of liver disease	286	RW018, 93-94
Work prevents alcohol consumption	287	RW018, 219-221
Didn't like the person he became when drinking	288	RW018, 248-251
Attributes diabetes to weight	289	PT019, 11-12
Operation/procedure causing reduction in alcohol	290	PT019, 67
Good knowledge/recall of liver cirrhosis	291	PT019, 131-134

Knowledge gained – unable to reverse cirrhosis	292	PT019, 214-216
Knowledge of liver disease gained from media	293	MW020, 68-70
'Scared' that drinking alcohol excessively	294	MW020, 89-93
Alcohol intake – same as peers/local environment	295	MW020, 94-96
Co-morbidity facilitates lifestyle change 'take care of self'	296	MW020, 176-179
Added alternatives to alcohol to life	297	MW020, 204-206

Appendix L: Preliminary Themes after initial analysis of 20 qualitative interviews

1/ Perceptions of Health Pre-Scan

- **Diabetes control – perceived as lack of previous symptoms/symptoms (vs. perception of health) Significant co-morbidity (e.g. pain)**
    - Limiting activity/exercise
- **Repeatedly abnormal liver blood tests**
    - Triggered awareness of possible liver problem
    - 'Left alone'/ignored by GPs prior to scan service
- **Agreeing to scan to identify problem early/early detection/monitoring**
- **Awareness of excessive alcohol**
- **Lifestyle/feelings of health pre-scan**
- **Concern/awareness of health pre-scan**

2/ Awareness of liver disease/Knowledge

- **Lack of knowledge of risk factor**
    - Liver disease just due to alcohol
    - 'Alcohol use causes diabetes'
    - Unaware diabetes/obesity leads to liver scarring
- **Improvement in liver disease knowledge**
    - Greater in abnormal scan vs normal → own reading, medical consultations
    - Confirming prior knowledge
- **Diabetes raised awareness of lifestyle/food content**

3/ Experience of Scan Process

- **Limited expectation pre-scan → lack of information**
- **Happy to be contacted for scan**
- **Non-invasive – quick/painless**
- **Convenience of scan in GP surgery vs hospital**
- **Immediacy of information**
    - Nurse explanation of advice/results
    - Numerical results from scan (liver stiffness number)
- **Recollection of results**
    - Underplaying of 'just abnormal' results
    - Recall bias
    - Preference of numerical scan value vs. categorical result

4/ Impact of abnormal scan result

- **Shock/Surprise**

    - Lack of symptoms
    - Lack of knowledge – 'only alcohol causes liver disease'
- **Anxiety**
    - Lack of understanding of results – 'went over my head/switching off during consultation' → improved with multiple consultations
    - Family/friend experience of liver cirrhosis
    - Progression of liver disease or death
    - Feeling alone – who to ask questions to?
    - Compounding other health issues
    - Reduced by prior knowledge of liver disease
- **Trigger to Lifestyle Change**
    - Awareness of own health
    - Contemplation of need to change
    - Prompting action → prevent liver getting worse
    - Not adopting lifestyle change – liver disease not seen to be significant problem
    - Symptoms

5/ Impact of normal scan result

- **Relief**
    - One less thing to worry about
    - Giving the all clear
- **Awareness of own health**
    - Lifestyle change even though no objective liver damage
    - Keeping liver healthy
- **Changes in liver scan (improvement)**
- **Surprise – awareness of risk/surprise at lack of damage**

6/ Lifestyle Change following liver scan

- **Facilitators of lifestyle change**
    - Support
        - Family
        - Education courses
        - Medical team – communication, making patients aware of risk
        - Alcohol team
    - Shock/anxiety of liver disease diagnosis
    - An active decision
- **Sustainability of lifestyle change**
    - Support/motivation
    - Making small/realistic changes
- **Barriers to lifestyle change**
    - Co-morbidity e.g. pain – unable to exercise/be active
    - Personal expectation – 'room for manoeuvre' in lifestyle
    - Life barriers – stress, habit, social life
    - Lack of information about liver disease/lifestyle available

7/ Follow-up of liver results

- **Repeating scan in future**
    - Reduce anxiety/ uncertainty of liver disease progression
    - Ensure ‘stay healthy’
    - Future modifications of lifestyle as required

8/ Miscellaneous

Appendix M: Presentations and Publications from PhD Thesis

Conference Oral Presentations:

1/ Non-invasive biomarkers unearth undiagnosed cirrhosis in the community.
BASL and AASLD 2013

David J Harman, Emilie A Wilkes, Martin W James, Stephen D Ryder, Guruprasad P Aithal, Indra Neil Guha

Awarded BASL Travel Award (Top 10 presentations by non-consultant grade presenters).

2/ Obesity and type 2 diabetes are predominant risk factors underlying previously undetected cirrhosis in the general population.

DDF 2015

David J Harman, Emilie A Wilkes, Martin W James, Stephen D Ryder, Timothy R Card, Guruprasad P Aithal, Indra Neil Guha

Awarded CORE Research Essay Prize, BASL Travel Award (Top 10 presentations by non-consultant grade presenters) and DDF prize for best oral presentation prize in Liver Free Papers session.

Research Articles:

1/ Direct targeting of risk factors significantly increases the detection of liver cirrhosis in primary care: a cross-sectional diagnostic study utilising transient elastography.

Harman DJ, Ryder SD, James MW, Jelpke M, Ottey DS, Wilkes EA, Card TR, Aithal GP, Guha IN.

BMJ Open. 2015 May 3;5(4):e007516. doi: 10.1136/bmjopen-2014-007516.

2/ A systematic review of the use of non-invasive tests in a community setting to stratify for alcoholic and non-alcoholic fatty liver disease

R Harris 1 , DJ Harman 1 TR Card 1, 2 , GP Aithal* 1 and IN Guha* 1

Under Review (Alimentary Pharmacokinetics and Therapy)

3/ Obesity and type 2 diabetes are predominant 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 *, Indra Neil Guha 1 * *=joint senior authors

(Under Review – Hepatology)