Doctoral statement

Defining and evaluating care for liver disease in UK Primary Care

Thesis for the degree of Doctor of Philosophy

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Abstract

Liver disease is an increasingly common cause of premature morbidity and mortality in the UK, primarily driven by alcohol (alcohol related liver disease (ALD)) and obesity (metabolic-dysfunction associated steatotic liver disease (MASLD), previously termed non-alcohol related fatty liver disease (NAFLD)). It is often diagnosed at the stage of decompensated cirrhosis, when interventions are less effective and mortality rates are very high. There are currently no standardised pathways of chronic disease management for patients with liver disease in UK primary care, limiting the potential for early detection and intervention.

Using a step-wise approach, this programme of work aimed to determine how best to deliver detection strategies for liver disease in the primary care setting. The six publications described in this thesis focus on four objectives, which were to: a) Define who is at risk of common chronic liver disease in the unselected general population; b)

Review current, UK community pathways of care for chronic liver disease; c) Explore the experiences of primary care practitioners in managing liver disease and d) Contribute to designing and implementing a primary care strategy for detection and management of liver disease.

A mix of methods were used to address these aims. Two systematic reviews of evidence from observational studies reported that most evidence on the metabolic risk factors for significant liver outcomes related to type two diabetes and obesity. Diabetes was found to more than double the risk of significant liver disease in MASLD. A narrative synthesis on the effect of moderate alcohol consumption in MASLD suggested that no safe level of alcohol could be recommended. An evidence review and national survey of current commissioning practice found stark inequalities in the provision of diagnostic tests and pathways of care for liver disease across the UK, with most areas having no pathways of care. Qualitative methods were used to explore the perceptions of general practitioners. They had little confidence in their own ability to manage liver disease, which they judged to be of low priority and high complexity. Further interviews with primary care practitioners guided by Normalisation Process Theory (NPT), elicited recommendations for implementation with incentivised, legitimate frameworks, and integration within other long term condition management. This research has contributed to a wider primary care strategy to detect and manage liver disease in practices in the North East of England. This is currently being piloted. Quantifying and researching the implementation outcomes of this strategy using a validated survey and interviews with health care practitioners and patients to guide national implementation will form the basis of my post-doctoral research.

Declaration:

I declare that this thesis is my own work and that I have correctly acknowledged the work of others. This submission is in accordance with University and School guidance on good academic conduct

I certify that no part of the material offered has been previously submitted by me for a degree or other qualification in this or any other University

I confirm that the word length is within the prescribed range as advised by my school and faculty. I confirm that this thesis contains collaborative work and my independent contributions have been outlined in the appropriate co-authorship forms found in this thesis.

Signature:

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Outputs during PhD Registration

The following published papers make up my thesis submitted for the degree of Doctor of Philosophy:

1. **Jarvis H,** Craig D, Barker R, Spiers G, Stow D, Anstee QM, et al. Metabolic risk factors and incident advanced liver disease in non-alcoholic fatty liver disease (NAFLD): A systematic review and meta-analysis of population-based observational studies. PLoS Med. 2020 Apr;17(4):e1003100.
2. **Jarvis H,** O'Keefe H, Craig D, Stow D, Hanratty B, Anstee QM. Does moderate alcohol consumption accelerate the progression of liver disease in NAFLD? A systematic review and narrative synthesis. BMJ Open. 2022 Jan 4;12(1):e049767.
3. **Jarvis H**, McPherson S, Anstee QM, Hanratty B. The pathway to better primary care for chronic liver disease. Br J Gen Pract. 2021 Apr 1 ;71(705):180–2.
4. **Jarvis H**, Worsfold J, Hebditch V, Ryder S. Engagement with community liver disease management across the UK: a cross-sectional survey. BJGP Open. 2021 Jul 5; BJGPO.2021.0085.
5. Standing HC, **Jarvis H**, Orr J, Exley C, Hudson M, Kaner E, et al. GPs' experiences and perceptions of early detection of liver disease: a qualitative study in primary care. Br J Gen Pract. 2018 Nov;68(676):e743–9.
6. **Jarvis H**, Sanders T, Hanratty B. Liver disease management as routine work in primary care: a qualitative interview study to guide implementation. Br J Gen Pract. 2022 Dec;72(725):e916–23.

The following article is contained in Appendix A and is currently under journal review at Chronic Illness. Long delays between submission and review have meant I am unable to submit the published paper within the body of this thesis. This article is directly relevant to my PhD thesis findings and should be read in series after published paper 6 where it adds to the qualitative research undertaken in chapter 4.

1. **Jarvis H,** Sanders T, Hanratty B. Liver disease as new work in the context of protocolised primary care - Do GPs have a role? A qualitative interview study.Chronic illness (under review)

The following published papers are not to be considered for assessment as part of my doctoral thesis but represent closely related work that I have been involved in developing and publishing (as a named author) during the time period of my PhD candidature.

Collaborative related working with the public, secondary care, professional bodies and policy makers to move from my PhD research to impact:

1. Williams R, Alexander G, Aspinall R, Batterham R, Bhala N, **Jarvis H**, et al. Gathering momentum for the way ahead: fifth report of the Lancet Standing Commission on Liver Disease in the UK. Lancet. 2018 Dec 1;392(10162):2398–412.
2. Williams R, Aithal G, Alexander GJ, Allison M, Armstrong I, **Jarvis H**, et al. Unacceptable failures: the final report of the Lancet Commission into liver disease in the UK. Lancet. 2020 18;395(10219):226–39.
3. Macpherson I, Abeysekera KWM, Harris R, Mansour D, McPherson S, Rowe I, et al. Identification of liver disease: why and how. Frontline Gastroenterol. 2022;13(5):367–73.

4. McPherson S, Armstrong MJ, Cobbold JF, Corless L, Anstee QM, Aspinall RJ, et al. Quality standards for the management of non-alcoholic fatty liver disease (NAFLD): consensus recommendations from the British Association for the Study of the Liver and British Society of Gastroenterology NAFLD Special Interest Group. Lancet Gastroenterol Hepatol. 2022 Aug;7(8):755–69
5. Schattenberg JM, Allen AM, **Jarvis H**, Zelber-Sagi S, Cusi K, Dillon JF, et al. A multistakeholder approach to innovations in NAFLD care. Commun Med (Lond). 2023 Jan 3;3(1):1.
6. McPherson S, **Jarvis H,** McGonigle J, Bedlington J, Dean J, Hallsworth K, et al. Stratification Of LIver Disease (SOLID): protocol for a prospective observational cohort study to determine the optimum biomarker strategies for the detection of advanced liver disease at the primary-secondary care interface. BMJ Open Gastroenterol. 2023 Feb;10(1):e001092.
7. Abeysekera KWM, Srivastava A, Rowe I*,* **Jarvis H** *et al.* Exploring changing attitudes to non-invasive liver fibrosis tests in secondary care pathways: comparison of two national surveys*Frontline Gastroenterology* Published Online First: 15 June 2023. doi: 10.1136/flgastro-2023-102415
8. Lazarus JV, Mark HE, Allen AM et al.Healthy Livers, Healthy Lives Collaborators. A global research priority agenda to advance public health responses to fatty liver disease. J Hepatol. 2023 Sep;79(3):618-634. doi: 10.1016/j.jhep.2023.04.035.

Co-investigator grant to research detection and management of Hepatitis C in UK primary care:

1. **Jarvis H**, Whiteley D. Eliminating hepatitis C: time to embrace primary care's critical role? Br J Gen Pract. 2021 Jun;71(707):250–1
2. Whiteley D, Speakman E, Elliott L, Davidson K, Hamilton E, **Jarvis H**, Quinn M, Flowers P. Provider-related barriers and enablers to the provision of hepatitis C

treatment by general practitioners in Scotland: A behaviour change analysis. J Viral Hepat. 2021 Mar;28(3):528-537.

3. Whiteley D, Speakman EM, Elliott L, **Jarvis H,** Davidson K, Quinn M, et al. Developing a primary care-initiated hepatitis C treatment pathway in Scotland: a qualitative study. Br J Gen Pract. 2022 Mar 21;BJGP.2022.0044.

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Chapter 1: Why is the detection and management of liver disease in primary care important?

1.1 Background and rationale

1.1.1 The increasing burden of liver disease

Liver disease is an increasingly common cause of morbidity and mortality in the UK and across the globe. This is primarily driven by increased consumption of alcohol and increasing numbers of people living with obesity and type 2 diabetes (leading to metabolic-dysfunction associated steatotic liver disease (MASLD), formally known as non-alcohol related fatty liver disease (NAFLD)). In the UK liver disease is now one of the leading causes of premature mortality (deaths in people under 65) and, unlike many other chronic diseases, morbidity and mortality rates are increasing (1). Liver disease is a disease of inequalities, with huge variation in outcomes across the UK linked to socioeconomic deprivation. Recent English data confirm ongoing increases in under 75s mortality from liver disease across the country, with huge disparities in morbidity and mortality rates with areas of Northern England and coastal communities experiencing a particularly high burden (2). The increasing burden of liver disease in the UK mirrors an increasing global burden, with marked growth in alcohol related liver harm (3) and MASLD (4). Globally, and in areas of the UK, chronic viral hepatitis is also a significant cause of chronic liver disease, but with national and global efforts to achieve elimination, viral hepatitis is beginning to contribute less to the ongoing liver disease epidemic (5).

Risk factors for the development of the common causes of chronic liver disease are well described. In England in 2021 there were 5686 premature deaths from liver disease related to alcohol consumption, accounting for 54% of all premature liver deaths (2). UK

recommendations for safe levels of alcohol consumption take into account all potential health consequences of consuming alcohol, but national guidelines recommend assessing for alcohol related liver harm in men consuming over 50, and women over 35, units of alcohol a week over a period of several months (6). According to the latest health survey for England data from 2021, this level of alcohol consumption is reported in 5% of all men over 18 and 2% of all women (7). The risk factors for the development of the other main cause of chronic liver disease in the UK (MASLD) are also well documented. People living with obesity, type 2 diabetes and other metabolic risk factors have an increased incidence of MASLD. Global estimates suggest that around 60% of people living with type 2 diabetes have fatty liver (8). The overall adult population prevalence of MASLD is estimated to be around 25% across Europe reflecting increasing levels of obesity, type 2 diabetes, dyslipidaemia and hypertension (the metabolic risk factors) (4). Evidence suggests that people living with higher numbers of metabolic risk factors are at increasing risk of MASLD, with estimated prevalence of MASLD of 80% in people with all five features of the metabolic syndrome (9).

The progression of MASLD to liver related morbidity and mortality is often slower than for alcohol related harm. A majority of people with fatty liver caused by metabolic risk factors will not die from liver disease. They are, however, at increased risk of cardiovascular disease (the commonest cause of death in MASLD) and other metabolic outcomes (10) and MASLD may have a significant effect on quality of life (11).

It is well recognised that a focus on primary prevention, including minimum unit pricing (MUP) for alcohol and a comprehensive obesity strategy, are of paramount importance. These public health measures are likely to have the greatest impact on harm from common liver diseases (12), but development of health policy in this area is hampered by competing interests. Efforts to shift population risk currently need to work in parallel with other secondary prevention strategies for those with established risk.

People with chronic liver disease in the UK currently present to medical services late, often at the stage of decompensated liver cirrhosis. As discussed, MASLD is very

common with known risk factors, but often a relatively benign clinical course, therefore there is significant challenge to identifying the minority at highest risk of these poor outcomes. Alcohol related liver disease (ALD) more often leads to poor liver disease outcomes, but despite established UK clinical guidelines around checking liver health in people drinking at harmful levels (13), these guidelines are not being routinely implemented (14).

1.1.2 New nomenclature to reflect a disease spectrum

In ALD and MASLD, the natural history from a healthy liver to cirrhosis passes through broadly similar histological stages. Steatosis (hepatic triglyceride content of >5%), steatohepatitis and fibrosis are common pathophysiological processes in both conditions. Risk factors for MASLD and ALD often coexist. The old nomenclature of NAFLD and ALD created mutually exclusive categories, unable to adequately reflect the common overlap and synergy these risks have in predicting liver disease progression (15). NAFLD was also a negative term (non-alcoholic), not reflecting the positive association of the condition with the metabolic syndrome (as outlined above (8,9)), and potentially stigmatising language. As a result of these concerns, three pan-national liver associations carried out a delphi process and developed a consensus statement introducing new nomenclature for chronic liver disease (16). An umbrella term of steatotic liver disease (SLD) includes both metabolic dysfunction associated steatotic liver disease (MASLD) and alcohol associated/related liver disease (ALD). There is also recognition of the role of dual aetiology, with a new term MetALD under the SLD umbrella for those with MASLD and increased alcohol intake.

The consensus statement on this nomenclature change (16) was only published in June of this year. MASLD is referred to throughout this thesis commentary rather than NAFLD. The papers making up this thesis were all published before this change was announced so refer to NAFLD throughout, and without mention of MetALD which was not in common use.

1.1.3 The current role of primary care in managing liver disease

The role of primary care in trying to improve the detection and management of liver disease is not well established. General practice in the UK has a central role in chronic disease management, with most people living with diabetes, chronic lung disease, cardiovascular disease and a range of other chronic conditions having an annual review of their health in primary care (often coordinated by the primary care nursing team). Liver health has not established itself as part of this proactive secondary prevention strategy. Detecting liver disease has not been a core part of the NHS health check (a 5 yearly health check carried out for adults between the ages of 40 and 74), with the recommendation to look for liver cirrhosis in people with high alcohol consumption a recent addition (17). There are no current, or historic, NHS incentive schemes paying general practitioners (GPs) to reach any targets or provide a standard of care for people with liver disease. This is despite a broad reaching framework (the quality and outcomes framework (QoF) (18) established for nearly 20 years for many other chronic conditions (19). In most areas of the UK, the role of primary care in managing liver disease is confined to acting on abnormal liver blood tests requested for a variety of reasons. Actions that follow liver blood tests in primary care are variable. Evidence points to some missed opportunities for diagnosing significant liver disease (20), but the majority of abnormal tests are not associated with any significant liver disease after extensive investigation (21). National guidelines on the management of abnormal liver blood tests have only recently been introduced (22).

In short, primary care has had a relatively small role in the management of liver disease. Changing population demographics with rapid rises in obesity and type 2 diabetes, as well as a continued culture of heavy alcohol consumption suggest that morbidity and mortality from liver disease will continue to rise, unless changes are made. Researching and implementing methods to improve earlier detection and interventions to tackle ongoing risk (secondary prevention) in primary care could be seen as a key factor in achieving this change.

1.1.4 Is earlier detection of liver disease beneficial?

Actively looking for asymptomatic liver disease at a population level with the aim of earlier detection and intervention may be considered a screening approach. Several of the prerequisites for such an approach (outlined by Wilson and Jungner (23) and updated by the 2015 UK national screening committee (24)), can be met for liver disease. Others are less clear.

As outlined above, liver disease is an important and increasing health problem in the UK. For the common causes of liver disease there is a well understood natural history of disease progression from healthy liver towards liver cirrhosis (25,26). There is also an asymptomatic stage prior to liver cirrhosis (liver fibrosis) which is known to be associated with liver disease morbidity and mortality (27,28). Liver fibrosis can now be detected using a combination of non-invasive tests (which will be discussed in more detail in chapter 3). This provides an opportunity for earlier intervention to prevent progression to cirrhosis. There is evidence that lifestyle modification (brief interventions and/or weight loss promotion) can be effective in reducing weight and alcohol intake (29,30), as well as producing improvements in liver biochemistry and histology (31,32). However, the evidence that these short term improvements translate into a reduction in liver disease morbidity and mortality is limited.

Currently gaps lie in the paucity of long-term data, our understanding of the possible risks of overdiagnosis, and uncertain acceptability of screening to patients and health-care providers. The high prevalence of risk factors, alongside the relatively low incidence of significant liver outcomes suggests that a case-finding approach *may* be a clinical and cost-effective strategy. How to select those at most risk in the general population, and how/if a case-finding strategy might work for earlier detection within current primary care structures are also research gaps. Whilst a high-risk case finding

approach is distinct from whole population screening, it is useful to consider the research gaps in this area based on screening prerequisites as the gold standard.

Figure 1 depicts current gaps in our knowledge around early detection of liver disease based on the first four sections of the 2015 UK National Screening Committee criteria (24). It also highlights where the research in this thesis aims to contribute to these knowledge gaps, to further elucidate the case for a high-risk population case finding approach.

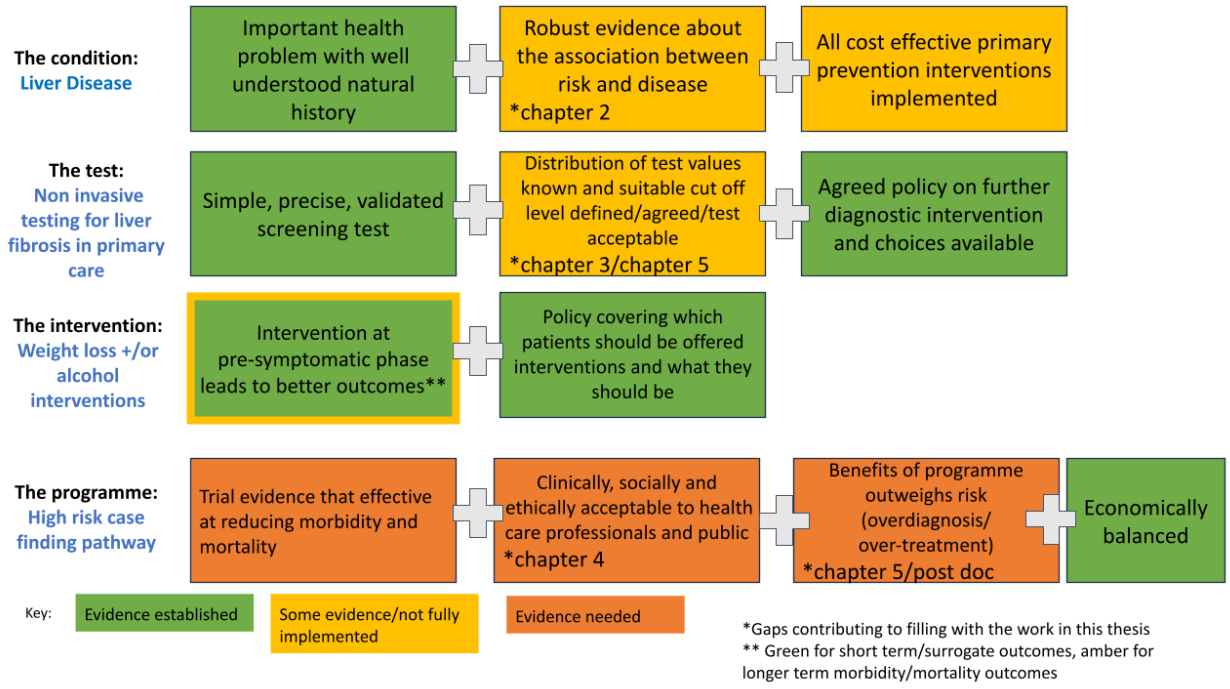

Figure 1: Current gaps in the evidence for an early detection strategy for liver disease in primary care, based on the 2015 UK National Screening Committee Criteria for population screening.

1.1.5 Health policy and research momentum in community liver disease management

The marked increase in mortality from liver disease in the UK is particularly obvious in the 30 years since 1990. During this time there was a 400% increase (33), prompting those working in health policy roles to take an interest in trying to address this. With no national strategy for liver disease and rapidly increasing mortality, the All-Party Parliamentary Hepatology Group (APPHG) published a timely report into improving outcomes in liver disease in 2014 (34). Their twenty recommendations included six directly relevant to tackling liver disease in primary care. A UK commission on liver disease was formed in collaboration with The Lancet in 2014. Clinical and policy recommendations followed over the next few years, focused on a need to improve liver disease detection and management in primary care (1,33,35,36). The first National Institute for Health and Care Excellence (NICE) guidelines (13,37) and quality standards (38) on aspects of liver disease were published in 2016-17 reflecting this increased national interest in improving care and outcomes.

The research recommendations in health policy documents, in addition to clinical guidelines are gradually leading to a shift in liver research away from hospital-based cirrhosis and liver transplant research, towards a focus on early detection and secondary prevention in the community. To date, this has been led by liver academics from secondary and tertiary centres and has focused on pathways advising on the sequence tests to find significant liver disease, guided by existing evidence around using these tests in the secondary care environment. A number of different approaches to detection in primary care have been studied; from an automated approach to interpretation of abnormal liver blood tests (39), to using blood tests which either indirectly or directly provide a measure of likely liver damage in those with abnormal liver blood tests (40), to basing the selection of those taken forward for specialist liver scans on known risk factors for disease, irrespective of initial abnormal blood tests (41). These strategies will be discussed in more detail in Chapter 3 of this thesis. They are introduced here to highlight that, although economic evaluations have found some

strategies to be clinically and cost effective (42,43), none of the pathways have been rolled-out beyond study areas. Input from primary care professionals in the development of these case-finding pathways has been minimal. Limited insight into the differences between the primary and secondary care context are obvious. A comprehensive approach to patient and public involvement in intervention development has also been lacking. These factors, coupled with a lack of consensus around the 'best' clinical pathway, may have hampered wider implementation efforts to date.

1.2 Thesis overview

1.2.1 Research Question(s)

Who should we be prioritising to best find people with significant liver disease in the community?

How should we be detecting and managing people with liver disease in the community?

What needs to be in place to develop effective and implementable pathways of care for liver disease in primary care?

1.2.2 Research Aims and objectives

The overall aim of this programme of work was to, using a step-wise approach, determine how best to deliver detection strategies for liver disease in the primary care setting. Specific objectives within this were to:

1. Define who is at risk of common chronic liver disease in the unselected general population

2. Review current pathways of care in the community for chronic liver disease in the UK

3. Research the experiences of primary care practitioners in managing liver disease and how this could become routine primary care work in:

    a) MASLD/ALD/unselected populations at risk
    b) Chronic viral Hep C (linked collaborative work on detection and management of viral hepatitis in primary care - see additional non-thesis published work)

4. Contribute to designing and implementing a primary care pathway for detecting and managing liver disease

5. Evaluate the implementation of an embedded pathway for liver disease management in the primary care setting from practitioner and patient perspectives*

*this objective will be completed during post-doctoral work (ethical and HRA permissions already granted)

1.2.3 Supporting chapters and papers

To support this thesis, there are six published papers embedded in six chapters.

Chapter one is an introduction to the thesis and why this body of work is important.

Chapter two aims to identify who is at most risk of common chronic liver disease in the unselected general population using evidence synthesis methods presented as two systematic reviews; one with a quantitative meta-analysis and one using narrative synthesis methodology.

This chapter includes: **published paper (PP) 1** (44) and **PP2** (45)

Chapter three synthesises current pathways of care in the community for chronic liver disease using data from published studies and a UK wide survey carried out as part of the thesis.

This chapter includes **PP3** (46) and **PP4** (47)

Chapter four presents qualitative research conducted with primary care health care professionals (HCPs) with particular emphasis on experiences of managing liver disease and how this may fit with other routine primary care work.

This chapter includes **PP5** (48)**, PP6** (49)

Chapter five summarises the process of intervention development using the above work to contribute to and plan an evaluation of an embedded pathway for liver disease management in primary care.

This chapter refers to the SOLID study protocol as a closely linked collaborative study (50).

Chapter six is a discussion of the main findings of the thesis work: summary, strengths and limitations, overall relationship to existing literature and clinical and research implications.

Chapter 2: Defining those at risk of common chronic liver disease in the unselected general population

This chapter presents findings from two systematic reviews looking to define and quantify the important risk factors for developing clinically significant liver disease in the general population. There is already a very well defined body of literature connecting high alcohol consumption to liver cirrhosis (51) and liver mortality (52) with in excess of a 9 fold increase in population mortality from liver disease in those drinking at very high levels (> 80g per day in men and >50g per day in women) (52). In view of this, the reviews in this chapter focus on important population risk factors for developing poor liver outcomes from MASLD, an area where there is still controversy around the use of risk factors to prompt liver assessments in the primary care setting.

To note that in the UK although ALD and MASLD are by far the commonest causes of chronic liver disease, there are also groups in the UK at risk of chronic viral hepatitis. The risk factors for chronic viral hepatitis are well defined with guidelines in place around testing in high risk groups (53). Defining those at risk of chronic viral hepatitis and other rarer causes of liver disease is not part of this main body of work.

People at risk of liver disease from whatever cause may have had blood tests done in general practice. Abnormalities in these tests are a ‘risk factor’ for liver disease (21) and there is a body of work looking at the value in using these abnormal tests to prompt further assessment in the primary care setting (54) and automating the process to help general practitioners interpret the results (39). The use and interpretation of abnormal liver blood tests is a separate, but connected, issue to the focus of this chapter. These tests need to be requested in *response* to a trigger (e.g knowing what the risk of liver disease is before requesting the test), and are part of the *process* of onward

assessment rather than a separate risk factor. Their interpretation is now subject to national guidelines in the UK (22). The way in which these tests contribute to pathways of care for liver disease in the UK is covered in the next chapter. However, no specific review was published as part of this thesis on liver blood tests as a population risk factor. Instead I considered the upstream metabolic risk factors that may or may not trigger these blood tests in primary care.

2.1 What are the risk factors for developing significant liver disease as a result of MASLD in the general unselected population?

2.1.1 Natural history and the interplay of environmental and genetic risk factors

The progression of liver damage in MASLD to liver related complications or mortality is determined by a number of factors. The presence of advanced fibrosis/cirrhosis on liver biopsy (defined histologically as F3 - bridging fibrosis or F4 cirrhosis) is a strong predictor of future poor clinical outcomes (55). Progression from steatosis to fibrosis/cirrhosis is however by no means universal, even in the presence of ongoing environmental risks. Less than 5% of MASLD patients die of liver related causes, behind both cardiovascular disease and extrahepatic malignancy (56). The role of the metabolic risk factors in predicting these outcomes is discussed below, but must be seen in the context of other risk factors including the role of the intestinal microbiome (57) and importantly the influence of genetic factors (58).

2.1.2 The role of the metabolic risk factors

The metabolic risk factors which make up the metabolic syndrome are widely considered to consist of insulin resistance/type 2 diabetes, abdominal obesity (either

measured as BMI, waist circumference or increased waist:hip ratio), dyslipidaemia (raised triglycerides/low high density lipoprotein (HDL)) and hypertension (59).

The majority of published work on the role of metabolic risk factors in predicting significant clinical liver outcomes (liver cirrhosis or liver mortality) has come from retrospective work on liver biopsy proven MASLD from secondary care cohorts (60,61). This work has been supplemented with data on histological outcomes in those with metabolic risk factors and MASLD using disease progression from paired liver biopsy studies (62,63). Primary care populations with much lower background prevalence of liver disease, yet high numbers with metabolic risk factors, are unlikely to be accurately represented when extrapolating risk from these studies. It is important that population level data on those with MASLD, and at risk of MASLD, are considered to know what effect the common metabolic risk factors have on clinically important liver disease outcomes. This is explored in **PP1**.

2.1.3 The role of moderate alcohol consumption in MASLD

Although there is clear evidence around the effects of *very* high levels of alcohol on poor liver outcomes, there remains debate around the role of moderate alcohol consumption in causing liver damage particularly in the presence of additional risk factors for liver disease. In the general population there is some evidence to suggest a protective effect of moderate alcohol consumption on the risk of *developing* MASLD (64), but other comprehensive reviews have outlined the bidirectional impacts of alcohol and the metabolic syndrome on developing progressive liver disease (65). From a primary care perspective the real question is around best advising our patients who have already been diagnosed with MASLD on alcohol consumption. Knowing if those who drink, and at what level, may be more at risk of significant liver damage is important, to be able to prioritise liver assessments and more targeted interventions.

The evidence in this area is contradictory and poorly defined hence the rationale for a comprehensive synthesis of this topic presented in **PP2**.

2.2 PP1 Metabolic risk factors and incident advanced liver disease in non-alcoholic fatty liver disease (NAFLD): A systematic review and meta-analysis of population-based observational studies

Jarvis H, Craig D, Barker R, Spiers G, Stow D, Anstee QM, Hanratty B. PLoS Med. 2020 Apr;17(4):e1003100. (44)

PLOS MEDICINE

RESEARCH ARTICLE

Metabolic risk factors and incident advanced liver disease in non-alcoholic fatty liver disease (NAFLD): A systematic review and meta-analysis of population-based observational studies

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Data Availability Statement: All relevant data are within the manuscript and its supporting information files.

Abstract

Background

Non-alcoholic fatty liver disease (NAFLD) is a leading cause of chronic liver disease worldwide. Many individuals have risk factors associated with NAFLD, but the majority do not develop advanced liver disease: cirrhosis, hepatic decompensation, or hepatocellular carcinoma. Identifying people at high risk of experiencing these complications is important in order to prevent disease progression. This review synthesises the evidence on metabolic risk factors and their potential to predict liver disease outcomes in the general population at risk of NAFLD or with diagnosed NAFLD.

Methods and findings

We conducted a systematic review and meta-analysis of population-based cohort studies. Databases (including MEDLINE, EMBASE, the Cochrane Library, and ClinicalTrials.gov) were searched up to 9 January 2020. Studies were included that reported severe liver disease outcomes (defined as liver cirrhosis, complications of cirrhosis, or liver-related death) or advanced fibrosis/non-alcoholic steatohepatitis (NASH) in adult individuals with metabolic risk factors, compared with individuals with no metabolic risk factors. Cohorts selected on the basis of a clinically indicated liver biopsy were excluded to better reflect general population risk. Risk of bias was assessed using the QUIPS tool. The results of similar studies were pooled, and overall estimates of hazard ratio (HR) were obtained using random-effects meta-analyses. Of 7,300 unique citations, 22 studies met the inclusion criteria and were of sufficient quality, with 18 studies contributing data suitable for pooling in 2 random-effects meta-analyses. Type 2 diabetes mellitus (T2DM) was associated with an increased risk of

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Competing interests: I have read the journal's policy and the authors of this manuscript have the following competing interests: QMA is coordinator of the LITMUS (Liver Investigation: Testing Biomarker Utility in Steatohepatitis) consortium funded by the IMI2 H2020 Framework Program of the European Union under Grant Agreement 777377; has been a consultant for 89Bio, Abbott Laboratories, Acuitas Medical, Allergan/Tobira, Altimmune, AstraZeneca, Axcella, Blade, BMS, BNN Cardio, Celgene, Cirius, CymaBay, EcoR1, E3Bio, Eli Lilly & Company Ltd., Galmed, Genentech, Genfit SA, Gilead, Grunthal, HistoIndex, Indalo, Imperial Innovations, Intercept Pharma Europe Ltd., Inventiva, IQVIA, Janssen, Madrigal, MedImmune, Metacrine, NewGene, NGMBio, North Sea Therapeutics, Novartis, Novo Nordisk A/S, Pfizer Ltd., Poxel, ProSciento, Raptor Pharma, Servier, Terns, Viking Therapeutics; and has received research support from Abbvie, Allergan/Tobira, AstraZeneca, GlaxoSmithKline, Glympse Bio, Novartis Pharma AG, Pfizer Ltd., Vertex. The other authors have declared that no competing interests exist.

Abbreviations: HDL, high-density lipoprotein; HR, hazard ratio; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; NCEP ATP III, National Cholesterol Education Program Adult Treatment Panel III; NICE, National Institute for Health and Care Excellence; T2DM, type 2 diabetes mellitus; WC, waist circumference; WHR, waist-to-hip ratio.

incident severe liver disease events (adjusted HR 2.25, 95% CI 1.83–2.76, $p < 0.001$, I^2 99%). T2DM data were from 12 studies, with 22.8 million individuals followed up for a median of 10 years (IQR 6.4 to 16.9) experiencing 72,792 liver events. Fourteen studies were included in the meta-analysis of obesity (BMI > 30 kg/m^2) as a prognostic factor, providing data on 19.3 million individuals followed up for a median of 13.8 years (IQR 9.0 to 19.8) experiencing 49,541 liver events. Obesity was associated with a modest increase in risk of incident severe liver disease outcomes (adjusted HR 1.20, 95% CI 1.12–1.28, $p < 0.001$, I^2 87%). There was also evidence to suggest that lipid abnormalities (low high-density lipoprotein and high triglycerides) and hypertension were both independently associated with incident severe liver disease. Significant study heterogeneity observed in the meta-analyses and possible under-publishing of smaller negative studies are acknowledged to be limitations, as well as the potential effect of competing risks on outcome.

Conclusions

In this review, we observed that T2DM is associated with a greater than 2-fold increase in the risk of developing severe liver disease. As the incidence of diabetes and obesity continue to rise, using these findings to improve case finding for people at high risk of liver disease will allow for effective management to help address the increasing morbidity and mortality from liver disease.

Trial registration

PROSPERO CRD42018115459.

Author summary

Why was this study done?

- This review gathered together the existing evidence on which metabolic risk factors are most associated with severe forms of liver disease.
- Many people have risk factors for developing fat on their livers, but most will not develop severe liver disease.
- Knowing which individuals are at greatest risk of liver disease will facilitate targeting of interventions to people with the greatest potential to benefit.

What did the researchers do and find?

- Combining the results of many individual studies, we found that type 2 diabetes was associated with a more than 2-fold increase in the likelihood of developing severe liver disease.
- Other metabolic risk factors (obesity, fat levels in the blood, and high blood pressure) were also reviewed. Obesity was also associated with an increased risk of liver disease, but to a lesser extent than type 2 diabetes.
- There was less information available on the other risk factors.

What do these findings mean?

- These findings mean that when health professionals are trying to find people at high risk of significant metabolic liver disease, they should focus on those who already have diabetes.
- The relative lack of evidence on the effects of other metabolic risk factors and combinations of these risk factors in predicting liver disease should be a focus of research in the future.

Introduction

Non-alcoholic fatty liver disease (NAFLD) is a leading cause of chronic liver disease worldwide, with an estimated population prevalence rate of up to 30% in Europe [1]. Progressive liver disease is asymptomatic and usually diagnosed late, at the stage of decompensated cirrhosis, when intervention is less effective and mortality rates are high. Most people with NAFLD will not develop progressive disease (advanced fibrosis/cirrhosis), but recent guidelines have stressed the importance of identifying the minority that will [2]. Data from biopsy studies have shown that the histological staging of liver fibrosis is one of the most important prognostic factors in NAFLD. Advanced fibrosis is associated with severe liver-related outcomes and increased mortality [3,4]. Without undertaking a biopsy, advanced liver disease can be ruled out with acceptable accuracy using non-invasive biomarkers or simple clinical scores [5,6]. However, validation of these methods in unselected populations is limited. Furthermore, in settings where the pretest probability of advanced fibrosis is low, the positive predictive value of non-invasive tests will fall and lead to many false positives [7]. This highlights a need to clearly define the at-risk population before employing these tests.

Case finding for advanced liver disease amongst adults with type 2 diabetes mellitus (T2DM) or metabolic syndrome is recommended by the European Association for the Study of the Liver (for those aged over 50 years) and the American Diabetes Association [2,8]. Ongoing studies are providing evidence for the clinical effectiveness and cost-effectiveness of risk-factor-based case finding for NAFLD in unselected populations [9–11]. However, the high and rising prevalence of risk factors for NAFLD means that the introduction of such programmes at scale will be costly, and neither the UK National Institute for Health and Care Excellence (NICE) nor the American Association for the Study of Liver Diseases has recommended case finding in primary care in their latest NAFLD guidelines [12,13]. In the absence of proactive case finding and assessment of high-risk individuals, case ascertainment is inconsistent and largely opportunistic, based on chance findings of abnormal blood tests or imaging carried out for other purposes. The current approach will not identify those at most risk. In many care settings, this means diagnosis late in the disease natural history, with limited scope for effective intervention [14].

In order to develop community-based strategies for earlier, targeted detection of liver disease, a good understanding is needed of which metabolic risk factors best predict severe NAFLD outcomes and advanced fibrosis. Research evidence published up until 2015 was synthesised to underpin the UK NICE guidelines [12], and this synthesis highlighted a paucity of evidence. Since then, several studies from large population cohorts have been published. In addition, the NICE review did not include all relevant outcomes. Cirrhosis and liver-related

mortality outcomes were omitted, though natural history studies suggest that it is reasonable to assume that people who develop liver cirrhosis or die from liver disease will have passed through the stage of non-alcoholic steatohepatitis (NASH) and advanced liver fibrosis. To address this gap in our understanding, we conducted an updated systematic review of published observational studies including all relevant outcomes. The aim was to synthesise evidence on which of the metabolic risk factors, or combination of risk factors, can best predict incident severe liver disease outcomes or NASH/advanced fibrosis in the general population at risk of NAFLD or with diagnosed NAFLD.

Methods

Registration of review protocol

The protocol for this review was registered in advance with PROSPERO (International Prospective Register of Systematic Reviews; CRD42018115459).

Types of studies and inclusion and exclusion criteria

Original studies were included if they were observational, prospective, or retrospective studies that reported either (1) severe liver disease outcomes (cirrhosis, complications of cirrhosis, or liver-related death) or (2) NASH/advanced fibrosis in adults ($\geq$18 years old) with metabolic risk factors as compared with adult individuals without metabolic risk factors. Metabolic risk factors were defined as those included in the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) definition [15], with the addition of BMI > 30 kg/m^2 as the most commonly measured obesity marker, assessed as individual risk factors or in combination, making up the metabolic syndrome.

We included both (1) studies where the cohort population had been predefined as having a diagnosis of NAFLD (based on ultrasound, coding, or abnormal liver blood tests in the absence of other diagnosed liver pathology) and (2) studies of general populations, if participants with risk factors for, or confirmed pathology from, alcohol, viral, or other liver disease were excluded or adjusted for.

The following types of studies were excluded: (1) studies where entry into the cohort was based on a tertiary referral and biopsy for clinical assessment of liver disease; (2) studies assessing only hepatocellular carcinoma as an outcome in the context of a non-cirrhotic liver; (3) studies using simple steatosis as an outcome; (4) studies performed in patients who had received liver transplants or were undergoing bariatric surgery; (5) studies where patients already had severe liver disease (as defined above) or NASH/advanced fibrosis at the time of cohort entry; and (6) studies that did not specifically report any odds ratio or hazard ratio (HR) with 95% CI for the outcome measure of interest.

We performed a systematic review following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [16] (see attached checklist [S1 Table]).

Search strategy and data extraction

Potentially relevant studies were identified through systematic literature searches of relevant databases (MEDLINE, EMBASE, the Cochrane Library, ClinicalTrials.gov, Conference Proceedings Citation Index–Science [CPCI-S; Web of Knowledge], and OpenGrey [http://www.opengrey.eu/]) in December 2018. No date or language restrictions were applied. Reference lists from potentially relevant papers and previous review articles were hand searched. MeSH (Medical Subject Headings) and free text terms for the metabolic risk factors and liver

outcomes of interest were used. The MEDLINE search strategy is available in S2 Table. Searches were updated in May 2019 and January 2020.

Two researchers (HJ and either GS or DS) independently screened titles and abstracts. Any disagreement in full-text selection was resolved by consensus. Record screening was also assisted by Rayyan, an online software tool that assesses similarities between selected records and highlights other potentially relevant studies based on the screener's previous selection [17]. Full texts of potentially relevant papers were obtained and read by 2 independent researchers with reference to the predefined set of criteria to determine final study inclusion. Data were extracted into a standardised, pre-piloted extraction form developed in Excel. For all studies, we extracted information on study design, source of data, prognostic factors of interest, outcomes of interest, and adjustment factors. Data extraction—undertaken by one researcher and checked by a second—was based on the updated Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modelling Studies checklist for prognostic studies (CHARMS-PF) [18].

Assessment of risk of bias

Two authors (HJ and RB) assessed the risk of bias independently. Since the included studies were observational cohort studies of prognostic factors, the QUIPS (Quality in Prognosis Studies) tool was used [18]. The QUIPS tool allows for quality assessment in 6 domains: study participation, study attrition, prognostic factor measurement, outcome measurement, adjustment for other prognostic factors, and statistical analysis/reporting. Risk of bias rating is reported as low, moderate, or high for each domain and then an overall risk of bias assigned based on the ratings in each domain. Any discrepancies in rating were addressed by a joint re-evaluation with a third author.

Data synthesis and analysis

The outcome measure for the meta-analysis was incident fatal and/or non-fatal severe liver disease in individuals with metabolic risk factors, in comparison with individuals without metabolic risk factors. The effect measures reported in the included studies were all HRs. The results of the studies were pooled, and an overall estimate of HR was obtained using a random-effects model. This model takes into account study heterogeneity, which was felt to be necessary from assessment of the clinical heterogeneity of the studies during data extraction, as well as the statistical heterogeneity as measured by the I^2 statistic. Where authors reported HRs for subgroups, a fixed-effects meta-analysis was first performed so a summary (pooled) HR could be included in the overall analysis. Publication bias was evaluated using visual inspection of funnel plots. Meta-analysis was carried out using Review Manager 5.3, Cochrane's meta-analysis software [19]. The prognostic factors with sufficient data and homogeneity between studies to carry out meta-analysis were T2DM and obesity (as measured by BMI). For each of these prognostic factors, severe liver disease outcomes were stratified into liver disease mortality, non-fatal severe liver disease events (cirrhosis and complications of cirrhosis), and a combined endpoint of both. Pre-specified sensitivity analyses were carried out to examine effect sizes when limiting the analysis to the following subgroups of studies: studies of participants with risk factors taken from a population with no previous diagnosis of NAFLD and studies with a low risk of bias as measured by the QUIPS tool. A narrative synthesis was conducted to expand on obesity as a prognostic factor of interest beyond BMI, and to summarise the evidence on the role of hypertension and lipid abnormalities in predicting advanced liver outcomes, as well as the evidence around combinations of metabolic risk factors for prognosticating advanced liver disease outcomes.

Patient and public involvement

An expert patient and public involvement group, including patients with late diagnosed NAFLD, were involved in the design of this review. They have had no role in the conduct or reporting of this review but will be actively involved in dissemination of the results to regional and national patient support groups.

Results

The searches identified 7,300 unique citations. Of the titles and abstracts screened, 267 articles were selected for full-text screening, where 245 were excluded for reasons reported in the PRISMA diagram (Fig 1). A total of 22 unique studies representing data from 16 cohorts were eligible for inclusion in the systematic review, and were assessed for quality [20–41]. Studies using data from the same cohort were only included if the sub-studies were assessing different prognostic metabolic factors.

Characteristics of included studies

Studies were included from Europe (Sweden [21,22,26–28,33,37,38], UK [20,32], Italy [20], Netherlands [20], and Spain [20]), North America (US [23,25,29–31,34,39–41] and Canada [36]), and Asia (Singapore [24] and China [35]), with data on over 24 million individuals. All the eligible studies were prospective or retrospective cohorts in design, and were all community-based general population cohorts, some defined by data linkage. In 16 of the studies, representing 12 of the cohorts, the included population was not pre-selected on the basis of a diagnosis of NAFLD, and liver-related outcomes were presumed to represent outcomes from severe NAFLD, as participants with evidence of other common causes of liver disease were either excluded at cohort entry or adjusted for in the analysis. All of the included studies excluded individuals drinking alcohol at harmful levels and those with alcohol-related liver disease at cohort entry, or adjusted for alcohol consumption during analysis. In 6 of the studies, representing 4 of the cohorts, part of the population under study had a predefined diagnosis of NAFLD, defined using ultrasound, abnormal liver blood tests, or International Classification of Diseases (ICD) coding at the time of cohort entry [20,25,31,38–40]. In 8 of the studies, the cohort studied included only men or women, but was otherwise an approximately general population. Thirteen of the studies looked at T2DM as a prognostic factor of interest, 14 looked at BMI, and 4 were interested in other measures of central obesity. Fewer studies assessed the effects of dyslipidaemia and hypertension as individual metabolic risk factors, with heterogeneity in prognostic factor definition and outcome of interest. Metabolic syndrome as a risk factor was studied in 4 studies, with 3 of them based on sub-cohorts from the same population cohort [25,39,40]. Of the 22 studies, 5 employed liver disease mortality as an outcome measure, 11 fatal and non-fatal severe liver disease events (combined endpoint), and 6 non-fatal severe liver disease events (cirrhosis/complications of cirrhosis). None of the included studies reported NASH/advanced fibrosis as outcome measures although these were included in the search strategy. Liver disease events were validated in all the studies by medical records and death certificates using ICD diagnosis codes. Of the 22 included studies, 13 received a low risk of bias rating using the QUIPS tool (S3 Table). Further details of included studies are shown in Table 1.

T2DM and the risk of incident severe liver disease events

Twelve studies were included in the meta-analysis of T2DM as a prognostic factor for incident severe liver disease. One study included in the review was excluded from the pooled primary

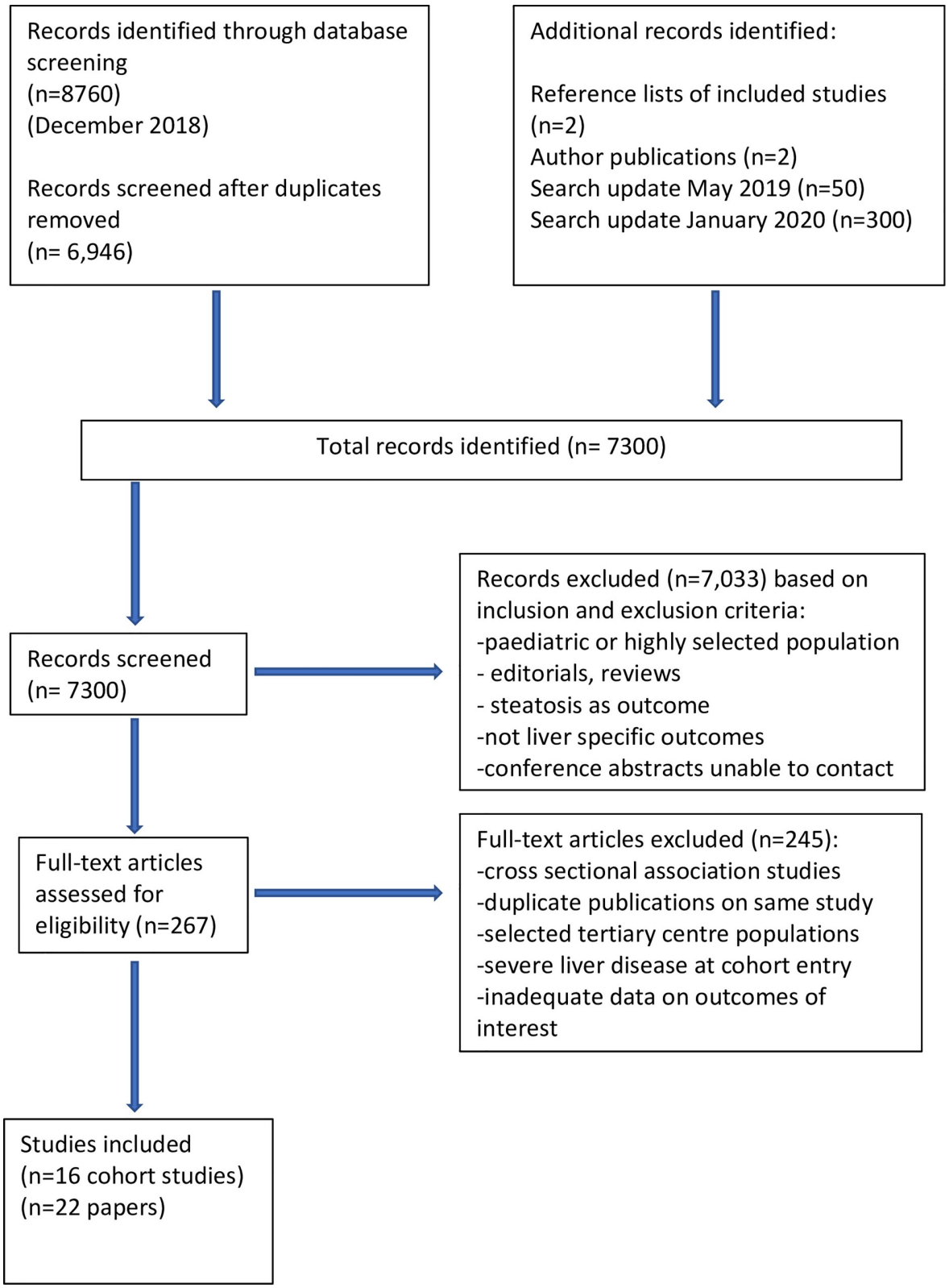

Fig 1. PRISMA diagram of study selection.

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Table 1. Characteristics of included studies.

Study	Country	Study design and population	Years of follow-up	Diagnosis of NAFLD at cohort inclusion	Metabolic RFs studied	Study outcomes of interest and number of events	Adjustments of interest considered	Adjusted HRs for liver events with 95% CIs and *p*-values	Risk of bias
Alexander 2019 [20]	UK, Netherlands, Italy, Spain	Retrospective data linkage cohort analysis, 18 million, 136,703 with NAFLD, mean age 55.8 years, 52% M	3.3	Yes (coding)	T2DM, BP, obesity	Cirrhosis/ complications, 7,375 events	Alcohol, other metabolic RFs	*BMI > 30: 1.03 (1.03–1.04), $p < 0.001$; T2DM: 2.86 (2.71–3.02), $p < 0.001$; high BP: 1.06 (1.00–1.12), $p = 0.03$	Low
Andreasson 2017 [21]	Sweden (Malmo cohort)	Prospective population cohort, 27,617, mean age 58.1 years, 38.8% M	19.8	No (exclusion of other causes of LD)	Obesity	Composite non-fatal and fatal LD, 505 events	Alcohol	*BMI > 30: 1.52 (1.17–1.98), $p = 0.002$; increased WC: women: 1.75 (1.32–2.33), $p < 0.001$, men: 1.69 (1.28–2.23), $p < 0.001$; increased WHR: women: 1.68 (1.36–2.07), $p < 0.001$, men: 1.78 (1.41–2.25), $p < 0.001$	Low
Björkström 2019 [22]	Sweden	Retrospective data linkage cohort analysis, 2.5 million, 406,770 with T2DM, mean age 64.7 years, 53.8% M	7.7	No (exclusion of other causes of LD)	T2DM	Composite non-fatal and fatal LD, 16,711 events	Unclear—high alcohol risk excluded at baseline	T2DM: 2.28 (2.21–2.36), $p < 0.001$	Low
El-Serag 2004 [23]	US	Retrospective data linkage cohort analysis, 173,643 with diabetes, 650,620 without diabetes, age > 20 years, 98% M (veterans)	10	No (exclusion of other causes of LD)	T2DM	Composite non-fatal and fatal LD, 7,799 events	Alcohol	T2DM: 2.15 (2.00–2.31), $p < 0.001$	Mod
Goh 2017 [24]	Singapore (Singapore Chinese Health Study)	Prospective population cohort, 63,247, age 45–74 years, 50% M	16.9	No (exclusion of other causes of LD)	T2DM, obesity	LD mortality, 133 events	Alcohol	T2DM: 2.6 (1.73–3.89), $p < 0.001$; BMI > 30: 1.36 (0.86–2.17), $p = 0.19$	Low
Golabi 2018 [25]	US (NHANES III)	Prospective population cohort, 3,613, median age 43 years, 50% M	19	Yes (ultrasound)	Metabolic syndrome	LD mortality, 22 events	Alcohol	1 MS RF: 26.35 (2.46–282.72), $p = 0.007$; 2 MS RF: 16.95 (1.59–180.91), $p = 0.019$; 3 MS RF: 1.98 (0.11–34.38), $p = 0.64$; 4 MS RF: 4.57 (0.32–64.88), $p = 0.26$	Mod
Hagström 2016[$] [26]	Sweden	Prospective population cohort, 44,248, age 18–20 years, 100% M (army conscripts)	37.8	No (exclusion of other causes of LD)	Obesity	Composite non-fatal and fatal LD, 393 events	Alcohol, BP	BMI > 30: 1.59 (0.64–3.95), $p = 0.32$	Mod
Hagström 2018 [27]	Sweden	Prospective population cohort, 1,220,2161, age 17–19 years, 100% M (army conscripts)	28.5	No (exclusion of other causes of LD)	Obesity, T2DM	Composite non-fatal and fatal LD, 5,281 events	High alcohol risk excluded at baseline, obesity, BP	T2DM: 3.49 (3.01–4.03), $p < 0.001$	Low

(*Continued*)

Table 1. (Continued)

Study	Country	Study design and population	Years of follow-up	Diagnosis of NAFLD at cohort inclusion	Metabolic RFs studied	Study outcomes of interest and number of events	Adjustments of interest considered	Adjusted HRs for liver events with 95% CIs and *p*-values	Risk of bias
Hagström 2019 [28]	Sweden	Retrospective data linkage cohort analysis, 1,185,733, mean age 28.6 years, 100% F (antenatal)	13.8	No (sensitivity analysis to exclude alcohol diagnoses)	Obesity, T2DM	Composite non-fatal and fatal LD, 852 events	Obesity, T2DM	BMI > 30: 1.76 (1.27–2.46), $p = 0.001$; T2DM: 4.30 (3.23–5.72), $p < 0.001$	Low
Ioannou 2003 [29]	US (NHANES I)	Prospective population cohort, 11,465, age 25–74 years, 50% M	13	No (exclusion of cirrhosis from other causes of LD)	Obesity	Composite non-fatal and fatal LD, 89 events	T2DM, cholesterol, alcohol	BMI > 30: 1.65 (0.9–3.1), $p = 0.11$	Low
Ioannou 2005 [30]	US (NHANES I)	Prospective population cohort, 11,434, age 25–74 years, 50% M	13	No (exclusion of cirrhosis from other causes of LD)	Obesity (central)	Composite non-fatal and fatal LD, 88 events	Alcohol	BMI > 30 and subscapular-to-triceps skinfold thickness ratio: high: 2.2 (1.1–4.6), $p = 0.026$, low: 0.8 (0.2–2.8), $p = 0.75$	Low
Kanwal 2019 [31]	US	Retrospective data linkage cohort analysis, 271,906, mean age 55.5 years, 94.3% M	9	Yes (abnormal blood tests) (exclusion of other causes of LD)	All metabolic risk factors	Cirrhosis, 22,794 events	Alcohol risk excluded at baseline and throughout follow-up period, other metabolic RFs	BMI > 30: 1.09 (1.06–1.13), $p < 0.001$; T2DM: 1.31 (1.27–1.34), $p < 0.001$; high BP: 1.59 (1.51–1.69), $p < 0.001$; dyslipidaemia (composite): 1.23 (1.19–1.28), $p < 0.001$; 2 MS RF: 1.33 (1.26–1.40), $p < 0.001$; 3 MS RF: 1.61 (1.53–1.69), $p < 0.001$; 4 MS RF: 2.03 (1.93–2.13), $p < 0.001$	Low
Liu 2010 [32]	UK (Million Women Study)	Prospective population cohort, 1,230,662, mean age 56 years, 100% F	6.2	No (exclusion of other causes of LD)	Obesity	Composite non-fatal and fatal LD, 1,811 events	Alcohol, BMI, T2DM	BMI > 30: 1.49 (1.33–1.68), $p < 0.001$; T2DM: 4.29 (2.74–6.73), $p < 0.001$	Low
Nderitu 2017 [33]	Sweden (AMORIS cohort)	Prospective population cohort, 509,436, mean age 44 years, 53.4% M	20	No (exclusion of other causes of LD)	All metabolic risk factors	Cirrhosis/ complications, 2,775 events	Other metabolic RFs	low HDL: 1.28 (1.04–1.59), $p = 0.020$; high triglycerides: 1.30 (0.99–1.72), $p = 0.059$; BMI > 30: 1.38 (0.93–2.04), $p = 0.11$; T2DM: 2.00 (1.19–3.38), $p = 0.009$	Mod
Otgonsuren 2013 [34]	US (NHANES III)	Prospective population cohort, 10,565, age 20–50 years, 45% M	13.8	Yes (ultrasound) (exclusion of other causes of LD)	Obesity	LD mortality, 26 events	Alcohol, BP, T2DM	BMI > 30: 1.06 (0.96–1.16), $p = 0.25$; WC: 1.02 (0.98–1.07), $p = 0.332$; WHR > 0.8: 83.51 (2.03–3,434.26), $p = 0.02$	Low
Pang 2018 [35]	China (China Kadoorie Biobank)	Prospective population cohort, 503,993, mean age 51.5 years, 41% M	10	No (exclusion of other causes of LD)	T2DM	Cirrhosis/ complications, 2,082 events	Alcohol, BMI	T2DM: 1.78 (1.45–2.18), $p < 0.001$	Mod

(*Continued*)

Table 1. (Continued)

Study	Country	Study design and population	Years of follow-up	Diagnosis of NAFLD at cohort inclusion	Metabolic RFs studied	Study outcomes of interest and number of events	Adjustments of interest considered	Adjusted HRs for liver events with 95% CIs and *p*-values	Risk of bias
Porepa 2010 [36]	Canada	Retrospective data linkage cohort analysis, 2,497,777, mean age 55.3 years, 56.3% M	6.4	No (exclusion of other causes of LD)	T2DM, BP, obesity	Cirrhosis/ complications, 8,365 events	BP, lipids, obesity, T2DM	T2DM: 1.77 (1.68–1.86), $p < 0.001$; high BP: 1.23 (1.14–1.31), $p < 0.001$; BMI > 30: 1.16 (1.01–1.33), $p = 0.03$	Low
Schult 2011 [37]	Sweden (Gothenberg survey)	Prospective population cohort, 855, mean age 50 years,100% M	40	No (exclusion of other causes of LD)	All metabolic risk factors	Composite non-fatal and fatal LD, 14 events	Alcohol	BMI > 30: 1.27 (1.09–1.48), $p = 0.002$; triglycerides: 1.99 (1.35–2.96), $p = 0.001$; other HRs not presented	Mod
Schult 2018 [38]	Sweden (Gothenberg survey)	Prospective population cohort, 1,462, age 38–60 years, 100% F	42	No (exclusion of other causes of LD)	Obesity (central)	Composite non-fatal and fatal LD, 11 events	Alcohol, BP	WHR > 0.8: 5.82 (1.59–21.4), $p = 0.008$	Mod
Simeone 2017 [39]	US	Retrospective data linkage cohort analysis, 18,754, age > 18 years, 38.5% M	2.3	Yes (coding) (exclusion of other causes of LD)	T2DM	Composite non-fatal and fatal LD, 5,645 events (any disease progression)	Unclear	T2DM: 2.0 (no CI given)	High
Stepanova 2010 [40]	US (NHANES III)	Prospective population cohort, 991, age > 17 years, 47.5% M	13.3	Yes (abnormal blood tests) (exclusion of other causes of LD)	All metabolic risk factors	LD mortality, 117 events	Alcohol, other metabolic RFs	T2DM: 1.05 (1–1.65), $p < 0.05$[@]; high cholesterol: 0.37 (0.06–2.15), $p = 0.284$; high BP: 0.07 (0.01–0.3x), $p = 0.007$; BMI > 30: 11.19 (2.43–51.56), $p = 0.002$; MS: 12.08 (1.10–132.22), $p = 0.042$	Mod
Younossi 2013 [41]	US (NHANES III)	Prospective population cohort, 1,448, age > 18 years, 64% M	16	Yes (ultrasound) (exclusion of other causes of LD)	Metabolic syndrome, obesity	LD mortality, 10 events	Metabolic RFs, alcohol	BMI > 30: 1.12 (1.03–1.21), $p = 0.008$; MS: 294.24 (118.74–729.14), $p < 0.001$	Low

BMI units are kg/m^2.

*Adjusted HR for whole cohort using a fixed-effects meta-analysis to get the combined HR from the 2 presented HRs for subgroups (coded versus uncoded combined in Alexander et al.; men and women combined in Andreasson et al.).

$Sub-cohort of the 2018 Hagström study but with additional data on alcohol consumption.

@CI and *p*-value as given in the paper presented here—different from the calculated CI used in meta-analysis using the HR and sample size (Fig 2). This difference is due to CI asymmetry in the published figures and inability to reproduce these figures on log transformation. Authors contacted to confirm data—no response.

BMI, body mass index; BP, blood pressure; CI, confidence interval; F, female; HDL, high-density lipoprotein; HR, hazard ratio; LD, liver disease; M, male; mod, moderate; MS, metabolic syndrome; NAFLD, non-alcoholic fatty liver disease; RF, risk factor; T2DM, type 2 diabetes mellitus; WHR, waist-to-hip ratio; WC, waist circumference.

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analysis as insufficient data were presented to support calculation of confidence intervals around the adjusted effect measure [39]. Overall, in the 12 observational studies, there were 22.8 million individuals followed up for a median of 10 years (IQR 6.4–16.9) experiencing 72,792 fatal and/or non-fatal severe liver disease events. Most of the studies included middle-

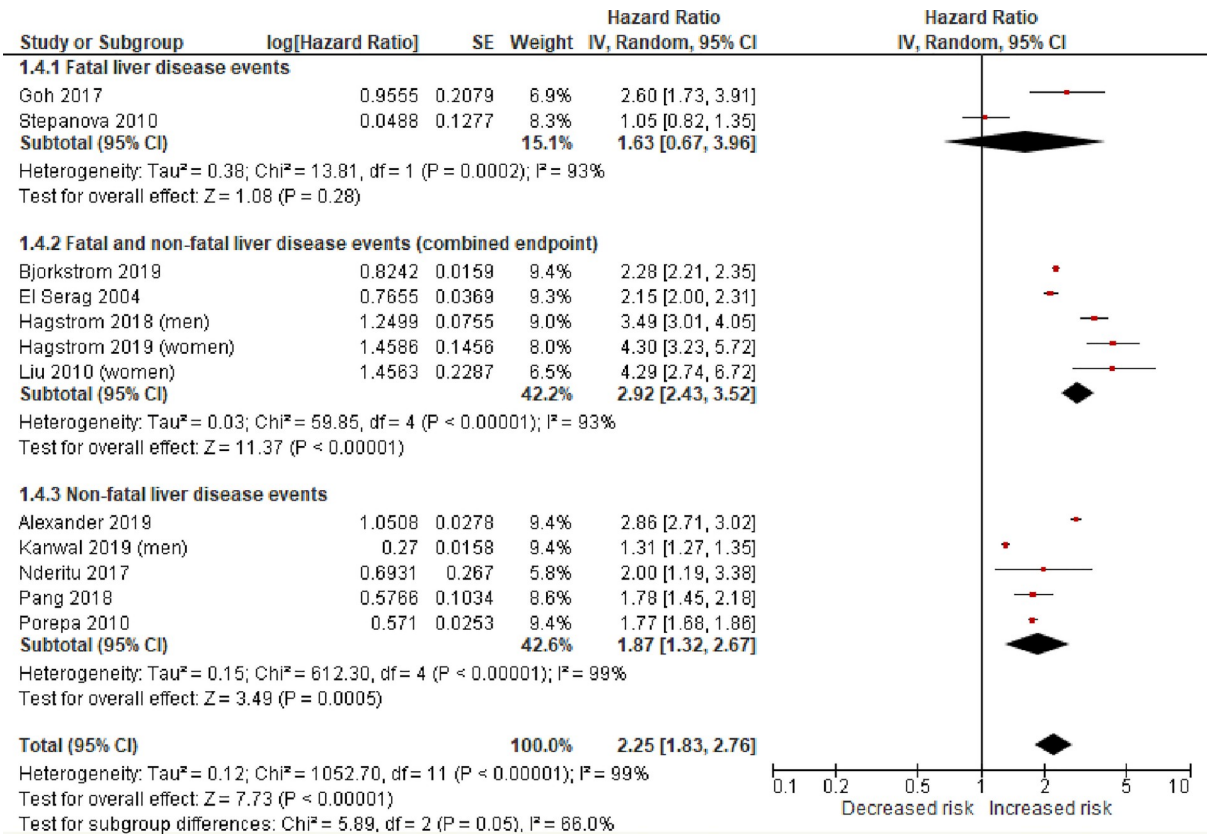

Fig 2. Random-effects meta-analysis of the risk of incident severe liver disease associated with type 2 diabetes. Statistical test for study heterogeneity = chi-squared test. Statistical test for summary effect in the meta-analysis = *Z* test. IV, inverse variance.

https://doi.org/10.1371/journal.pmed.1003100.g002

aged individuals, with 7 studies including male and female individuals in roughly equal numbers, 2 studies including only women, and 3 only/predominantly men.

The individual study and pooled estimates of the association between T2DM and risk of severe liver disease are shown in Fig 2. T2DM was significantly associated with an increased risk of severe liver disease events (random-effects HR 2.25, 95% CI 1.83–2.76, $p < 0.001$, I^2 99%). There was no asymmetry of the funnel plot to suggest a publication bias (S1 Fig).

Obesity and the risk of incident severe liver disease events

Fourteen studies were included in the meta-analysis of obesity as a prognostic factor for incident severe liver disease. The definition of obesity used for the meta-analysis was a BMI > 30 kg/m^2 as this was the most widely reported metric used. Some of the included studies, and others, also looked at alternative measures of obesity risk, such as waist-to-hip ratio (WHR). There were too few studies to pool these results, but the findings are reported in the narrative synthesis below. The 14 observational studies in the meta-analysis provided data on 19.3 million individuals followed up for a median of 13.8 years (IQR 9.0 to 19.8) experiencing 49,541 fatal and/or non-fatal severe liver disease events. Nine of the studies of predominantly middle-aged individuals included men and women in roughly equal numbers. Two studies looked at women only, with 1 of the cohorts recruiting women in the early stages of pregnancy only [28]. The 3 remaining studies recruited predominantly men—1 at army conscription (ages 18–20 years), producing a younger study population at baseline, with follow-up for nearly 40 years [26].

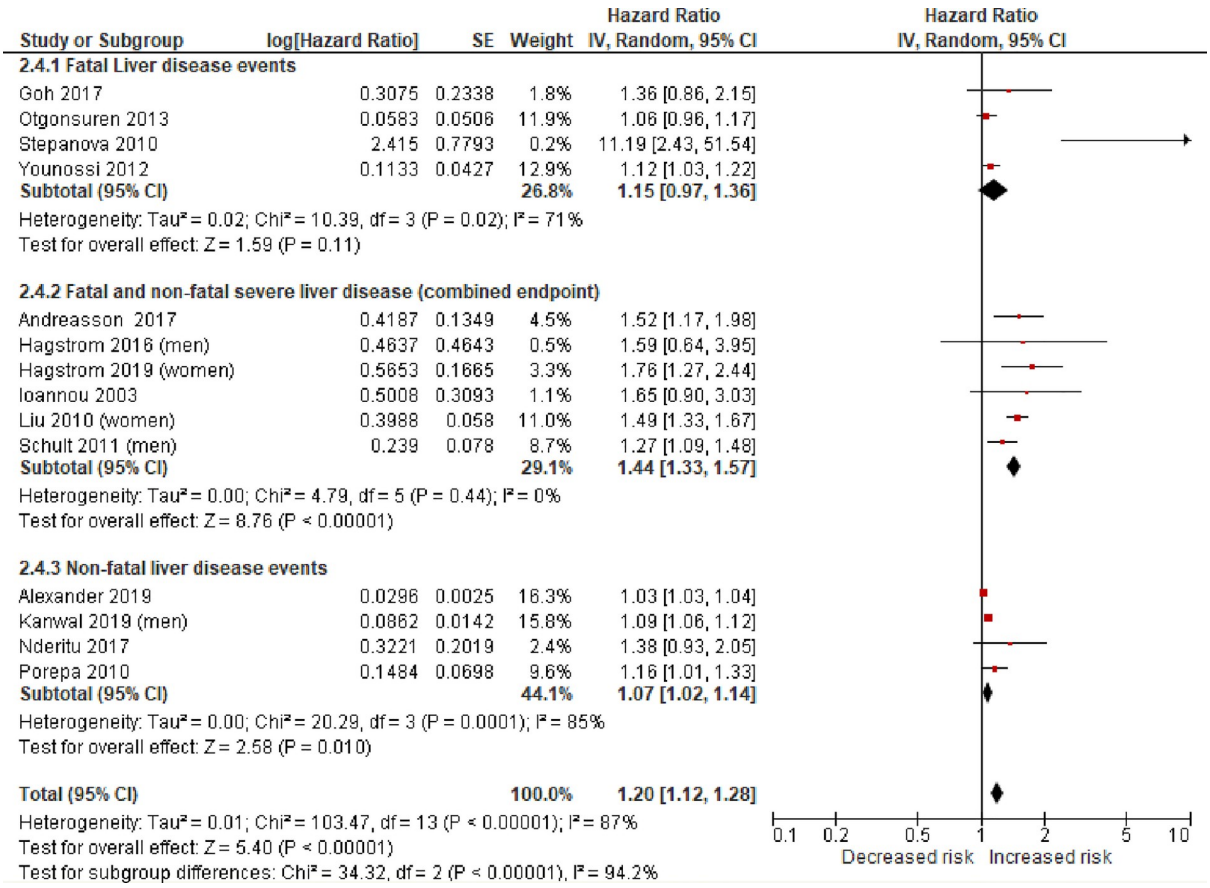

Fig 3. Random-effects meta-analysis of the risk of incident severe liver disease associated with obesity (BMI > 30 kg/m^2). Statistical test for study heterogeneity = chi-squared test. Statistical test for summary effect in the meta-analysis = *Z* test. IV, inverse variance.

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The individual and pooled estimates of association between obesity (BMI > 30 kg/m^2) and risk of severe liver disease are shown in Fig 3. A BMI > 30 kg/m^2 was associated with an increased risk of severe liver disease events (random-effects HR 1.20, 95% CI 1.12–1.28, $p < 0.001$, I^2 87%). There was some asymmetry of the funnel plot, suggesting possible under-publishing of smaller negative studies (S2 Fig).

Sensitivity analyses

Limiting the analysis to studies judged to be at low risk of bias and excluding studies where NAFLD was diagnosed at cohort entry provided overall estimates consistent with the primary analysis for both prognostic factors that were meta-analysed (Table 2). The high levels of heterogeneity, as indicated by the high I^2 values, were explored. These were felt to be due to the variation in study design, particularly around the range of populations and outcomes studied, leading to clinical heterogeneity. Despite this, there was a consistent direction of effect, and, based on the objective of the review, pooling using meta-analysis was still felt to be appropriate.

Other measures of central obesity

Four studies looked at alternative measures of central obesity as possible prognostic factors for severe liver disease outcomes. One prospective cohort examined the subscapular-to-triceps

Table 2. Risk of fatal and/or non-fatal severe liver disease events associated with T2DM and obesity: Sensitivity analyses.

Analysis	Number of comparisons	Overall adjusted HR with 95% CI	I^2 value
T2DM and risk of severe liver disease			
Including only those with no previous diagnosis of NAFLD at cohort entry	10	2.54 (2.19–2.94), $p < 0.001$	96%
Including only studies with low risk of bias using QUIPS tool	8	2.59 (1.99–3.36), $p < 0.001$	99%
BMI > 30 kg/m^2 and risk of severe liver disease			
Including only those with no previous diagnosis of NAFLD at cohort entry	11	1.29 (1.14–1.46), $p < 0.001$	87%
Including only studies with low risk of bias using QUIPS tool	10	1.18 (1.10–1.26), $p < 0.001$	89%

CI, confidence interval; HR, hazard ratio; NAFLD, non-alcoholic fatty liver disease; QUIPS, Quality in Prognosis Studies; T2DM, type 2 diabetes mellitus.

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skinfold thickness ratio (SFR) as a measure of central obesity [30], concluding that in obese individuals (BMI > 30 kg/m^2), only those with a SFR > 1 were at increased risk of a combined fatal/non-fatal severe liver disease outcome (HR 2.2, 95% CI 1.1–4.6, $p = 0.026$). Two studies reported the association between waist circumference (WC) and liver disease events [21,34], with 1 of the studies (using a combined fatal/non-fatal endpoint) reporting that a WC over 88 cm in women was a better predictor of liver outcomes than BMI (HR for BMI > 30 kg/m^2: 1.3, 95% CI 0.4–1.88, $p = 0.16$; HR for WC > 88: 1.75, 95% CI 1.32–2.33, $p < 0.001$), but that this was not the case for men [21]. The other study found no significant association between WC and liver disease deaths, but did not stratify results by sex [34]. Two studies analysed the relationship between WHR and severe liver disease outcomes. One study focused on women and, using a combined fatal/non-fatal endpoint, found a strong association between a WHR > 0.8 and severe liver disease (HR 5.82, 95% CI 1.59–21.4, $p = 0.008$). Only a small number of the nearly 1,500 cohort participants had diabetes recorded at cohort entry ($n = 13$), and no incident diabetes was recorded during follow-up. The lack of meaningful adjustment for diabetes was felt to be a study weakness [38]. The other study reporting WHR as a prognostic factor again found this central obesity measure to prognosticate better than BMI in women only, with the HR being nearly identical to that for BMI > 30 kg/m^2 in men. For women, the HR was 2.05 (95% CI 1.49–2.82, $p < 0.001$) for those with a WHR more than 0.05 above normal [21]. There were insufficient similar studies to be able to pool any of the results, but the available data suggest that measures of central obesity are better at prognosticating for severe liver disease outcomes than BMI alone, particularly in women.

Other metabolic risk factors and the risk of severe liver disease events

Lipids. Five studies investigating lipid levels, and their prognostic value for liver disease outcomes, looked at low high-density lipoprotein (HDL), high triglycerides, combined lipid abnormalities, and hypercholesterolaemia as exposures of interest, with varying cutoff points for 'abnormality', so direct comparison and pooling was not attempted. By far the largest study that looked at low HDL and high triglycerides as independent risk factors, in line with cutoffs for a diagnosis of metabolic syndrome, examined an unselected population of over 100,000. This study reported a HR for a non-fatal severe liver disease event of 1.28 for low HDL (95% CI 1.04–1.59, $p = 0.02$) and 1.30 for high triglycerides (95% CI 0.99–1.72, $p = 0.059^*$; analysis done on a smaller dataset of 65,000 with available complete data) [33]. A large population-based data linkage study of over 270,000 individuals (over 95% male) supports these findings, with a reported HR of 1.23 (95% CI 1.19–1.28, $p < 0.001$) for an outcome of cirrhosis using a combined dyslipidaemia exposure based on low HDL and/or high triglycerides [31]. This suggests a smaller adjusted effect of these metabolic risk factors compared to the effect of T2DM, perhaps similar to the adjusted effect of a BMI > 30 kg/m^2, but is based on few studies.

Hypertension. Four studies reported on hypertension as a prognostic factor of interest in predicting severe liver outcomes. A mortality study looking at individuals with presumed NAFLD (based on abnormal liver blood tests) found a negative association after adjustment for other metabolic risk factors (HR 0.07, 95% CI 0.01–0.3, $p = 0.007$) [40]. This is contradicted by 2 larger population-based data linkage studies looking at non-fatal severe liver disease, which both report a positive association between diagnosed hypertension and an incident liver outcome with HRs of 1.23 (95% CI 1.14–1.31, $p < 0.001$) [36] and 1.59 (95% CI 1.51–1.69, $p < 0.001$) [31]. This association was supported, although with a much smaller effect size, by findings of a study using several large European primary care datasets to report non-fatal liver outcomes (HR 1.06, 95% CI 1.00–1.12, $p = 0.03$) [20].

Metabolic syndrome. Three articles reported on the association between metabolic syndrome (NCEP ATP III definition) [15] and liver mortality using data from the same population cohort study [25,40,41], with 1 additional study looking at combined metabolic risk with cirrhosis as the outcome [31]. The effect sizes in the mortality data are inconsistent, with very wide confidence intervals, despite the studies representing the same population. One of the studies reported a weakening of the association of metabolic risk factors with liver-related mortality with increasing number of metabolic risk factors [25]. The other 2 analyses concluded that metabolic syndrome ($\geq$3 metabolic risk factors) was associated with an increased risk of liver-related mortality, with reported HRs of 12.08 (95% CI 1.10–132.22, $p = 0.042$) [40] and 294.24 (95% CI 118.74–729.14, $p < 0.001$) [41]. A more recent, larger population data linkage study looked in detail at combinations and numbers of metabolic risk factors associated with cirrhosis outcomes, reporting increasing HRs for increasing numbers of risk factors, with a HR of 2.56 (95% CI 2.26–2.92, $p < 0.001$) for those with T2DM, obesity, hypertension, and dyslipidaemia [31].

Discussion

In this systematic review and meta-analysis of 22 studies including data from over 24 million individuals, we found that T2DM was significantly associated with incident severe liver disease, with a more than 2-fold increase in the combined outcomes studied (random-effects HR 2.25, 95% CI 1.83–2.76, $p < 0.001$, I^2 99%). There was a less marked association between obesity and incident severe liver disease using BMI > 30 kg/m^2 as the obesity measure (random-effects HR 1.20, 95% CI 1.12–1.28, $p < 0.001$, I^2 87%), with a suggestion that other measures of central adiposity may better predict poor liver outcomes, particularly in women.

There were many fewer studies looking at the relationship between other metabolic risk factors and incident severe liver disease, with differing definitions of prognostic factors of interest. Pooling of results was therefore not appropriate, but the suggestion from the largest, highest quality studies was that lipid abnormalities (low HDL and high triglycerides) and hypertension are both independently associated with incident severe liver disease. The adjusted effect sizes appear to be similar to that for high BMI. Fewer data were available looking at combinations of metabolic risk factors making up the metabolic syndrome as a predictor of liver outcomes, with a suggestion from the largest study of an increase in non-fatal liver outcomes in those with metabolic syndrome of a similar magnitude to that for T2DM.

The presented review focuses on general population data, aiming for the results to be applicable for clinicians seeing unselected patients. Studies of individuals with biopsy-proven NAFLD at cohort entry have been criticised due to the inherent bias of selecting patients who have been referred for liver biopsy, and the relatively short median follow-up time. These studies, however, provide important comparative and supportive evidence.

Studies looking at metabolic risk factors in patients with biopsy-proven NAFLD and long-term severe liver disease outcomes have found strong independent associations between

T2DM at the time of biopsy and liver-related outcomes [4,41–43]. HRs for T2DM as a predictor of severe outcomes in these studies vary more widely, partly due to the inclusion of all-cause mortality in some of the studies, where the commonest cause of death was cardiovascular disease rather than liver-related mortality. Studies specifically reporting liver-related outcomes clearly report T2DM as the most important clinical risk factor, reporting HRs between 2.19 (95% CI 1.00–4.81) [43] and 22.83 (95% CI 2.97–175.03) [44] for liver-related mortality. These studies generally do not report other metabolic risk factors as independent predictors of poor outcome, although smaller sample sizes may indicate they were not powered adequately to detect these smaller risk increases.

A significant body of related research has come from paired sequential liver biopsy studies looking at the association between metabolic risk factors and histological NAFLD progression. A systematic review of 11 paired biopsy studies (411 individuals) published in 2015 indicated that only hypertension was significant in predicting the rate of histological progression between biopsies (odds ratio 1.94, 95% CI 1.00–3.74) [45]. In line with our findings, more recent studies, including the largest single-centre biopsy cohort to date, identified T2DM as the strongest metabolic predictor of histological disease progression [46,47].

A large body of work has been extensively reviewed and synthesised on the epidemiology and natural history of NAFLD. The focus of these reviews is distinct yet complementary to our work. They identify the high and rising global burden of NAFLD and associated adverse outcomes using prevalence data from cross-sectional studies of people with a confirmed diagnosis of NAFLD. These reviews estimate the global prevalence of NAFLD in people with diabetes to be more than double that of the general population (55.48% versus 25.2%) [1,48,49]. A recent meta-analysis looking at NAFLD in T2DM reported prevalence estimates for NASH of 37.3% and advanced fibrosis of 17% in those with T2DM, far higher than general population estimates of these progressive forms of NAFLD [49]. This review adds to these prevalence data, indicating that the rate of incident severe liver outcomes is also significantly higher in those with T2DM.

It is noteworthy that despite our outcome inclusion criteria including NASH and advanced fibrosis, none of the included studies reported these earlier disease stages as outcomes. This leaves information on the association between metabolic risk and NASH/advanced fibrosis coming from cross-sectional and highly selected populations [48]. As NASH and advanced fibrosis have traditionally been histological diagnoses requiring a liver biopsy, this is not surprising and may explain the paucity of evidence reported in a similar review of the ability of NAFLD risk factors to predict progressive disease in the population [12].

In this synthesis we included data from population cohorts without a definite clinical diagnosis of NAFLD at baseline. It is therefore possible that not all liver outcomes in these groups were due to underlying NAFLD, which is a study limitation. All included studies reported that people with known liver disease of other common aetiologies (which would include viral hepatitis) were excluded and have adjusted for alcohol in the analysis. However, the possibility of other undiagnosed pathologies cannot be fully excluded. A recent multi-site European cohort study found that metabolic risk factors predicted cirrhosis with similar effect sizes for people with and without a coded diagnosis of NAFLD [20] and suggested this was likely due to NAFLD not being diagnosed or accurately coded (i.e., hidden disease in the control group). Other studies have also reported lower than expected levels of diagnostic coding for NAFLD [50]. This suggests that our approach may be a strength, as only a minority of people living with NAFLD have had a formal diagnosis, and so represent a highly selected subgroup.

The limitations of synthesising observational data, including the issue of unmeasured confounding, are well known, and the clinical and statistical heterogeneity described in this review

was not unexpected. We also acknowledge the possibility of publication bias. However, this was a large study, including data on over 24 million individuals with over 300 million person years of follow-up. Use of predetermined inclusion and exclusion criteria and robust quality assessment mean we have included the best available evidence to report on the outcome of incident advanced liver disease related to metabolic risk.

Identifying those at risk of severe liver disease in the community setting will only be beneficial if effective lifestyle interventions and/or liver-targeted medications are effective and available. We have increasing evidence for the clinical effectiveness of lifestyle interventions in NAFLD [51,52], 1 compound already has demonstrated efficacy in a phase III trial [53], and several other promising liver-targeted medications are also in phase III studies [54]. There is also an increasing evidence base around the cost-effectiveness of earlier case finding in the community setting [11,55]. These advances highlight the timely nature of this review, which can help guide clinicians and primary care policy-makers towards selecting the patients most likely to benefit from these interventions. Future research should focus on studying prospective population cohorts for earlier liver outcomes and their relationship to metabolic risk, including the interplay of these risk factors in combination. With increased availability of non-invasive methods to look for advanced fibrosis, looking at earlier outcomes will become both more realistic for research studies and, more importantly, more relevant for clinicians managing unselected populations who are looking to target, diagnose, and manage those at increased risk of poor outcomes before they develop decompensated cirrhosis.

In conclusion, this robust meta-analysis provides evidence to suggest that people with T2DM have a significantly increased risk of future severe liver disease and that obesity (as measured by BMI) also has an impact on risk. More evidence is needed around the interplay of metabolic risk factors (metabolic syndrome) in predicting severe liver outcomes in people at risk of NAFLD. Our findings support a more structured, risk-factor-based approach in NAFLD management, particularly for patients with T2DM.

Supporting information

S1 Fig. Funnel plot of studies included in the T2DM meta-analysis.
(TIF)

S2 Fig. Funnel plot of studies included in the obesity meta-analysis.
(TIF)

S1 Table. PRISMA checklist.
(DOCX)

S2 Table. MEDLINE search strategy.
(DOCX)

S3 Table. Risk of bias of included studies.
(DOCX)

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Transparency declaration: I (HJ) confirm that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained. No ethical approval was required for this systematic review.

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Supervision: Dawn Craig, Quentin M. Anstee, Barbara Hanratty.

Writing – original draft: Helen Jarvis.

Writing – review & editing: Dawn Craig, Robert Barker, Gemma Spiers, Daniel Stow, Quentin M. Anstee, Barbara Hanratty.

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2.2.1 PP1 commentary

In this comprehensive systematic review and meta-analysis, including data on over 24 million individuals, I found that type 2 diabetes was the most studied and important risk factor of the metabolic risk factors to predict the risk of advanced liver disease. In those at risk of MASLD, the presence of diabetes led to a greater than two-fold (random-effects HR 2.25, 95% CI 1.83 -- 2.76, $p < 0.001$, I^2 99%) increase in the liver cirrhosis/mortality. The effect of obesity as measured by BMI on liver outcomes was less marked (random-effects HR 1.20, 95% CI 1.12–1.28, $p < 0.001$, I^2 87%), although it remained significant, with an indication that other measures of obesity, particularly waist:hip circumference may be more important predictors. Less data was available on the other components and combinations of the metabolic syndrome. It would appear that having diabetes is a key factor, as important as metabolic risk factors in combination.

This represents the largest review in this area carried out with systematic methodology and including sensitivity analysis and risk of bias assessments. It was designed to be directly applicable to clinicians seeing unselected patients (such as in primary care) by including only general population cohorts. This is in contrast to the frequently cited evidence on the effect of diabetes in MASLD which relies on evidence from patients from tertiary liver clinics (62). These findings support a more structured, risk-factor-based approach in MASLD management, particularly for patients with type 2 diabetes.

2.3 PP2 Does moderate alcohol consumption accelerate the progression of liver disease in NAFLD? A systematic review and narrative synthesis

Jarvis H, O'Keefe H, Craig D, Stow D, Hanratty B, Anstee QM. BMJ Open. 2022 Jan 4;12(1):e049767. (45)

BMJ Open

Does moderate alcohol consumption accelerate the progression of liver disease in NAFLD? A systematic review and narrative synthesis

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ABSTRACT

Objectives Liver disease is a leading cause of premature death, partly driven by the increasing incidence of non-alcohol-related fatty liver disease (NAFLD). Many people with a diagnosis of NAFLD drink moderate amounts of alcohol. There is limited guidance for clinicians looking to advise these patients on the effect this will have on their liver disease progression. This review synthesises the evidence on moderate alcohol consumption and its potential to predict liver disease progression in people with diagnosed NAFLD.

Methods A systematic review of longitudinal observational cohort studies was conducted. Databases (Medline, Embase, The Cochrane Library and ClinicalTrials.gov) were searched up to September 2020. Studies were included that reported progression of liver disease in adults with NAFLD, looking at moderate levels of alcohol consumption as the exposure of interest. Risk of bias was assessed using the Quality in Prognostic factor Studies tool.

Results Of 4578 unique citations, 6 met the inclusion criteria. Pooling of data was not possible due to heterogeneity and studies were analysed using narrative synthesis. Evidence suggested that any level of alcohol consumption is associated with worsening of liver outcomes in NAFLD, even for drinking within recommended limits. Well conducted population based studies estimated up to a doubling of incident liver disease outcomes in patients with NAFLD drinking at moderate levels.

Conclusions This review found that any level of alcohol intake in NAFLD may be harmful to liver health. Study heterogeneity in definitions of alcohol exposure as well as in outcomes limited quantitative pooling of results. Use of standardised definitions for exposure and outcomes would support future meta-analysis. Based on this synthesis of the most up to date longitudinal evidence, clinicians seeing patients with NAFLD should currently advise abstinence from alcohol.

PROSPERO registration number The protocol was registered with PROSPERO (#CRD42020168022).

Strengths and limitations of this study

- This is a timely synthesis of the best available evidence on the role of moderate alcohol consumption in non-alcohol-related fatty liver disease.
- We used systematic searches to identify literature and prospectively registered our protocol on PROSPERO.
- We restricted our inclusion criteria to studies that used longitudinal data to provide evidence of temporal associations.
- Due to heterogeneity in definitions of alcohol exposure and outcomes, it was not possible to carry out a meta-analysis.
- The existing literature base is limited and only six studies were sufficiently robust to meet our predefined inclusion criteria.

INTRODUCTION

Liver disease is an increasing health burden across the world, and it is now a major cause of premature (<65 years) mortality.[1 2] As premature mortality rates from many non-communicable diseases have fallen over the last 30 years, the burden of liver disease is increasing.[2 3] The most common causes of chronic liver disease in high-income countries are alcohol-related liver disease (ARLD) and metabolic-syndrome-related liver disease (or non-alcohol-related fatty liver disease—NAFLD). Chronic liver disease is often diagnosed as a result of abnormal liver blood tests or liver imaging, with a fatty liver (steatosis) progressing in some through inflammation (steatohepatitis) and stiffening (fibrosis) to scarring (cirrhosis) increasing the risk of decompensated liver disease or liver cancer. This process of progressive damage to the liver is common to both aetiologies.

While the labelling of liver disease suggests a dichotomy, the clinical reality is that there is significant overlap between ARLD and NAFLD.[4] The incidence of obesity and diabetes is rising, and a substantial proportion of the population is drinking alcohol at above recommended limits.[5]

Table 1 International definitions of moderate alcohol consumption, UK recommended limits and levels that would warrant assessment for alcohol-related liver disease, all expressed in grams of alcohol and UK units

	Grams of alcohol		UK units of alcohol	
Definitions:	**Daily***	**Weekly***	**Daily***	**Weekly***
Accepted International consensus of moderate alcohol consumption	**F: <20** **M: <30**	F: <140 M: <210	F: <2.5 M: <3.75	F: <17.5 M: <26.25
UK recommended safe weekly limits	≤16	112	≤2	**≤14**
NICE thresholds for assessing for liver cirrhosis	F: >40 M: >57	F: >280 M: >400	F: >5 M: >7.1	**F: >35** **M: >50**

*Daily and weekly figures are given for comparison only. The bold numbering for each definition is the standard format in which this definition is expressed
NICE, National Institute of Health and Care Excellence.

It is estimated that up to 17% of the adult population may meet criteria for both NAFLD and ARLD.[6] Despite this, there is little guidance available for generalist healthcare professionals, on how to advise people with a diagnosis of NAFLD on safer alcohol consumption.

Recommendations on safe alcohol consumption levels vary worldwide. Increasingly, they take into account the effect that alcohol has on the risk of developing many adverse health outcomes, including cancer. International analysis suggests this should be as low as total abstinence to minimise all health risks.[7] Recommended limits for safe alcohol consumption in the UK general population are up to 14 units of alcohol per week in both men and women,[8] which equates to 16 g of alcohol per day at 8g/unit. Moderate alcohol consumption is generally defined in the literature as drinking within, or slightly in excess of, these limits versus complete abstinence.[4] There is a significant gap between this recommended 'moderate' limit and the levels of alcohol consumption that would prompt an assessment for alcohol-related liver damage. The UK National Institute of Health and Care Excellence (NICE) recommends offering a liver cirrhosis test to men drinking over 50 units and women drinking over 35 units a week on an ongoing basis over several months,[9] leaving a significant proportion who are drinking at and above 14 units a week, but below the levels to have liver assessment based on their alcohol consumption alone. The international differences in definition of how many grams of alcohol a 'unit' contains can create confusion and the reader is directed to table 1 to help in interpreting the study results in the context of UK Government and NICE recommended limits.

There is still uncertainty, and an absence of guidance, on safe levels of alcohol consumption for people with established NAFLD. Indeed, it is not clear that any level of alcohol consumption is safe to minimise progression of the liver disease in this population. It is known that people with very high levels of alcohol consumption (who would meet criteria for a diagnosis of ARLD), and who also have metabolic risk factors, are at even greater risk of adverse liver outcomes.[10 11] But there is also some evidence that for people with metabolic risk factors (but who do not have a NAFLD diagnosis), drinking alcohol at low levels may protect against cardiovascular disease, prevent fatty liver disease and lead to better outcomes than with complete abstinence.[12 13] Elucidating the role of alcohol in NAFLD progression is a small part of understanding the interplay of genetic and environmental factors and their effects on the liver; an area of ongoing research and debate.[14]

The purpose of this systematic review is to synthesise evidence on the role of moderate alcohol consumption on progression to severe liver disease in people with diagnosed NAFLD. This will help guide the advice given to NAFLD populations around safe alcohol consumption in primary care and specialist settings.

METHODS

The protocol for this review was registered in advance with PROSPERO (International Prospective Register of Systematic Reviews, #CRD42020168022).

Types of studies, inclusion and exclusion criteria

Primary studies were included if they were prospective or retrospective cohort studies. The population of interest was adult patients (>18 years old) with diagnosed NAFLD. The outcome of interest was progression of liver disease in this population. The exposure of interest was no versus moderate alcohol consumption. For our inclusion criteria we defined 'moderate consumption' as up to 35 units per week in females, and 50 units per week in males (levels that would be considered the threshold for definite risk of ARLD according to NICE guidelines[9]). This definition included studies that focused on the effects of alcohol within or just above current weekly recommended limits (the usual definition of moderate alcohol consumption), as well as those who looked beyond these levels of consumption, up to the NICE ARLD levels.

Exclusion criteria were as follows: (1) studies where the population had diagnosed ARLD; (2) studies where the population was defined according to their alcohol consumption levels rather than their NAFLD status at baseline; (3) studies where patients already had severe liver disease at the time of cohort entry; (4) cross-sectional studies or studies where exposure was only measured at the same time as outcome.

We performed a systematic review following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[15]

Search strategy and data extraction

Potentially relevant studies were identified through systematic literature searches of relevant databases (Medline, Embase, The Cochrane Library and ClinicalTrials.gov, Conference Proceedings Citation Index—Science, Web of Knowledge, CINAHL(EBSCO)) in January 2020 and updated in September 2020. No language restrictions were applied, and databases searched documents published from 1990 onwards. Reference lists from potentially relevant papers and previous review articles were hand searched. Medical Subject Headings and free-text terms for the NAFLD population, alcohol exposures and liver outcomes of interest were used. Two researchers (HJ and either HO'K or DS) independently screened titles and abstracts. Any disagreement in full-text selection was resolved by consensus. Record screening was also assisted by Rayyan, an online software tool that assesses similarities between selected records and highlights other potentially relevant studies based on the screener's previous selection.[16] Full texts of potentially relevant papers were obtained and read by two independent researchers with reference to the predefined set of criteria to identify final study inclusion. Data were extracted into a standardised form, piloted on three studies before full extraction. Data extraction was based on the updated checklist for critical appraisal and data extraction for systematic reviews of prediction studies checklist for prognostic studies,[17] undertaken by one researcher and checked by a second. Two authors (HJ, HO'K) assessed the risk of bias independently. Since the included studies were observational cohort studies of prognostic factors, the Quality in Prognostic factor Studies tool was used.[18]

Data synthesis

Pooling of data was not possible due to exposure and outcome heterogeneity across studies. A narrative synthesis[19] was undertaken, with data synthesised by alcohol exposure level. Due to the small number of studies, even those with high risk of bias are included in the synthesis, although this bias assessment is made clear throughout the narrative.

Patient and public involvement

Patients and the public were not involved in the design or conduct of this review but will be involved in the dissemination of findings through a funded PPI steering group and close collaboration with the British Liver Trust.

RESULTS

The searches identified 4578 unique citations. Of the titles and abstracts screened, 42 articles were selected for full-text screening. Thirty six were excluded at this stage for reasons summarised in the PRISMA diagram (figure 1). In seven of the excluded studies, the population did not have a baseline diagnosis of NAFLD[20–26] and in five studies the population already had advanced liver disease at baseline.[27–31] Five of the excluded studied focused on non-liver specific outcomes such as overall mortality,[32–36] while 11 were conference abstracts or short papers which held inadequate data on either population, exposure or outcomes.[20 21 23 25 29 32 33 37–40] The most common reason for exclusion at full-text stage was study design, mainly cross-sectional studies looking at a single time point to assess exposure and outcome.[24 30 31 37–39 41–47] There were also eight studies which on full-text reading were review articles or editorials.[48–55] A total of six unique studies representing data from five cohorts were eligible for inclusion in the systematic review, and were assessed for quality (figure 1).[56–61]

Characteristics of included studies

Further details of included studies are shown in table 2.

Within the studies meeting inclusion criteria, three[58–60] looked at the exposure of alcohol consumption up to, or similar to, the accepted international definition of moderate consumption. This is <20 g/day in women and <30 g/day in men.[26] Three of the studies[56 57 61] looked at low alcohol consumption but also extended moderate consumption up to levels of alcohol consumption which would be considered more consistent with ARLD.

Moderate alcohol consumption (accepted international definitions) and risk of liver disease progression in NAFLD

Three studies examined the effects of alcohol in NAFLD using definitions in keeping with the accepted international definition of moderate consumption.[58–60] Although these studies shared a similar aim, they varied in NAFLD population definition, measurement of alcohol consumption and choice of liver outcomes. Two looked at histological progression outcomes and one used non-invasive indirect blood-based markers of liver fibrosis. Two of the studies were rated as having a low risk of bias[59 60] and one was rated as having a moderate risk.[58]

Ajmera *et al*[58] studied a NAFLD population taken retrospectively from the non-alcohol related steatohepatitis (NASH) clinical research network, including populations from an observational study and the placebo arm of two NASH drug trials, all of whom had biopsy proven NAFLD (285 participants). Alcohol consumption was measured at cohort entry and at varying time points up to, and including, follow-up liver biopsy, which occurred, on average, 3.9 years later. Multiple histological markers of disease progression and resolution were studied, and the authors looked at the association between baseline drinking status and disease, as well as change in drinking status over time and disease progression/resolution. For most of the histological end points studied, there was no significant difference between moderate drinkers and abstainers in outcomes, with the only significant results suggesting that abstainers had less progressive or a higher likelihood of resolution of their disease between biopsies, particularly the persistent abstainers when compared with

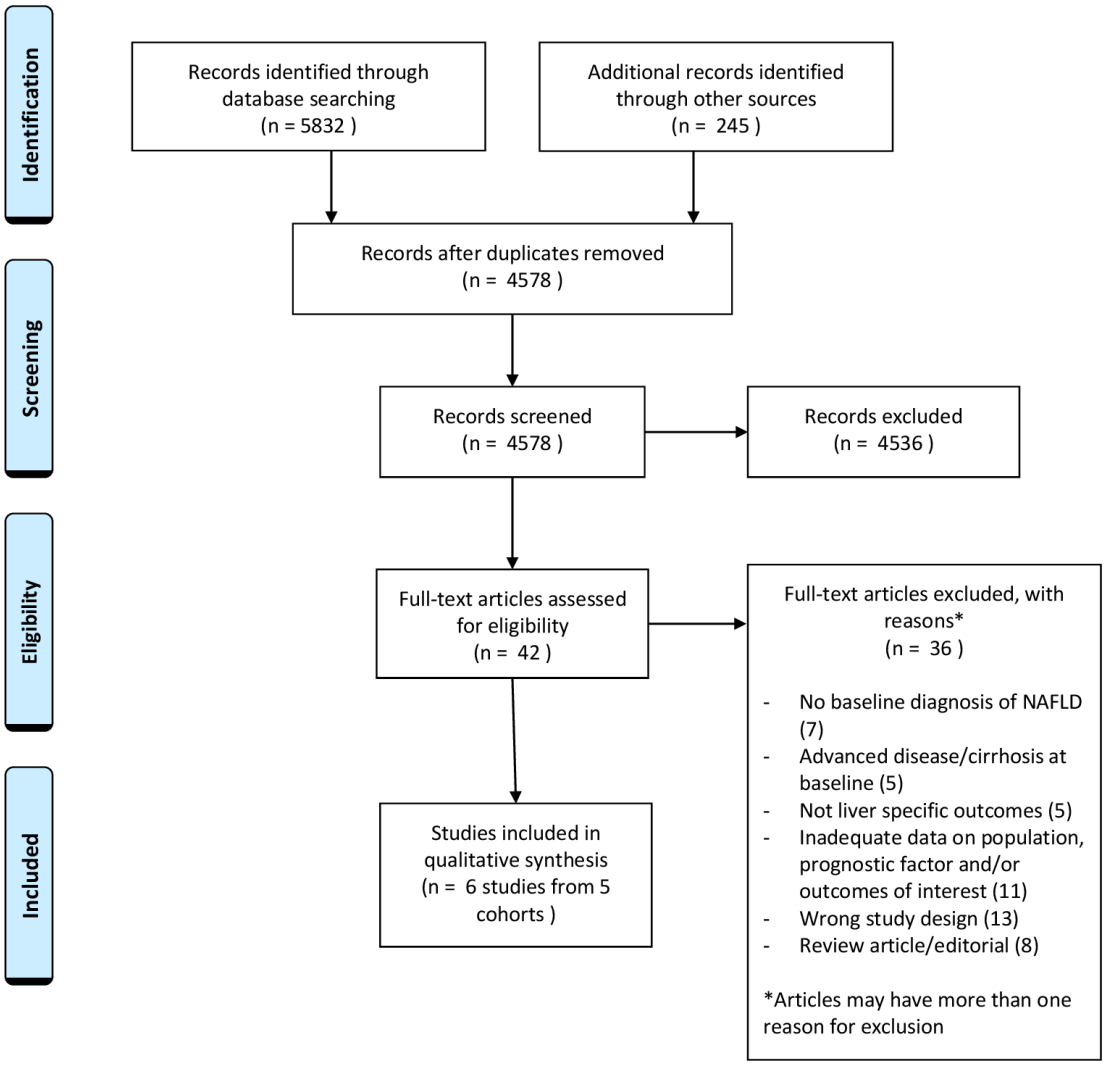

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram of study selection. NAFLD, non-alcohol-related fatty liver disease.

the persistent moderate drinkers. Results should be interpreted in the knowledge that a large number of related histological outcomes were reported, increasing the likelihood of a statistically significant result by chance. The study also had a relatively short follow-up period between biopsies. The absence of detailed information on which other prognostic factors were taken into account, led to a rating of moderate on risk of bias assessment.

A similar study by Ekstedt *et al*[60] looked at a smaller group (71 participants) of biopsy proven NAFLD, with follow-up histology an average of 13.8 years after initial biopsy. Alcohol consumption was assessed at baseline and follow-up, with heavy episodic drinking assessed in addition to weekly consumption. Primary outcome was significant fibrosis progression, defined as progression by one or more fibrosis stage or the development of end stage liver disease during follow-up. Although higher weekly alcohol consumption showed some tendency to predict fibrosis progression (OR for increase in grams of alcohol per week 1.012 (1.000 to 1.025)) only the presence of heavy episodic drinking (defined as >60 g/day in men and >48 g/day in women more than once a month) reached statistical significance in predicting fibrosis progression.

Of note in both the Ajmera and Ekstedt studies were the very low levels of alcohol consumption in the 'moderate drinkers', with the majority (78%) of the moderate drinkers drinking less than monthly in the Ajmera study and the average weekly alcohol consumption in the Ekstedt study being only 39 g/week. Both studies also included a significant number of patients who already had liver inflammation (NASH) at baseline (over 50% in both studies), indicating a higher proportion of patients with a tendency to progressive disease as compared with a general NAFLD population, as would be expected with biopsy-based studies.

In contrast to the relatively selective biopsy studies, Chang *et al*[59] studied a large prospective population cohort (Kangbuk Samsung Health Study) of whom 58 927 had ultrasound evidence of fatty liver but without evidence of other liver diagnoses or advanced disease. Alcohol exposure was weekly units at baseline and follow-up was for a median of 8.3 years with outcome of interest being

Table 2 Characteristics of included studies

Author /year	Country	Study design and population	Yrs f/u	Method of NAFLD diag*	Method of measuring alcohol consumption	Definition of moderate consumption studied as RF	Study outcomes of interest and event no	Adjustments of interest considered	Adjusted HRs/OR/ mean differences for liver events with 95% CI and p values	Risk of bias
Åberg 2019[56]	Finland	Retrospective data linkage cohort analysis NAFLD population 6462, mean age 53 years, 60% M	10.9	FLI>30	Questionnaire at cohort entry	<50 g/day in 10 g categories with abstinence as reference	Composite non-fatal and fatal liver disease 58 events	? unclear other than age, sex	Per increase in 10 g of alcohol per day versus abstinence HR 1.43 (1.12 to 1.82) p=0.004	High
Åberg *et al* 2020[57]	Finland (FINRISK Health survey)	Retrospective data linkage cohort analysis NAFLD population 8345, mean age 53.7 years, 60% M	11.1	FLI>60	Questionnaire at cohort entry (recall for past month)	<50 g/day in 10 g categories with abstinence as reference	Composite non-fatal and fatal liver disease 152 events	Age, sex, smoking, T2DM	g alcohol/day versus abstinence 0–9 hour 1.38 (0.74 to 2.58) 10–19 hour 2.18 (1.04 to 4.53) 20–29 hour 3.62 (1.67 to 7.76) 30–39 hour 3.53 (1.53 to 8.14) 40–49 HR 8.79 (3.95 to 19.56)	Low
Ajmera *et al* 2018[58]	USA	Retrospective analysis of longitudinal cohorts within NASH CRN NAFLD population 285, mean age 47 years, 30% M	3.9	Liver biopsy	Questionnaire at cohort entry (Skinner lifetime drinking history)	<2 drinks per day and excluded if >6 drinks on 1 occasion ≥monthly	Histological resolution or progressionon follow-up biopsy	Age, sex, race, smoking	Persistent moderate drinkers versus abstinence* **resolution** of NASH: OR 0.32 (0.11 to 0.92) p=0.04 fibrosis progression: adj mean diff 0.00 (−0.29 to 0.29) p=0.99	Mod
Chang *et al* 2019[59]	South Korea (Kangbuk Samsung Health Study)	Prospective population cohort NAFLD population 58 927, mean age 37.7, 82% M	4.9	US	Questionnaire at each study visit (annual or biennial)	10–19.9 g/day (F) 10–29.9 g/day (M) (low 1–9.9 g/day)	Fibrosis progress as estimated by high indirect serum scores**	Age, sex, BMI, smoking, exercise level, education, T2DM, BP	Mod versus abstinence† (repeat observations) Fib4: HR 1.33 (1.13 to 1.57) NFS: HR 1.37 (1.23 to 1.52) low versus abstinence (repeat observations) Fib 4: HR 1.08 (0.91 to 1.27) NFS: HR 1.14 (1.02 to 1.27)	Low

Continued

Table 2 Continued

Author /year	Country	Study design and population	Yrs f/u	Method of NAFLD diag*	Method of measuring alcohol consumption	Definition of moderate consumption studied as RF	Study outcomes of interest and event no	Adjustments of interest considered	Adjusted HRs/OR/ mean differences for liver events with 95% CI and p values	Risk of bias
Ekstedt *et al* 2009 [60]	Sweden	Retrospective cohort NAFLD population 71, mean age 47.3, 72% M	13.8	US and liver biopsy	Questionnaire AUDIT-C and interview at follow-up	g/day—no upper limit defined as 'moderate'	Fibrosis progress on follow-up biopsy	Age, sex, BMI, T2DM, fibrosis at baseline	Increasing alcohol g/week versus abstinence OR 1.012 (1.000 to 1.025) p=0.055	Low
Kawamura *et al* 2016 [61]	Japan	Prospective cohort NAFLD population 9959, mean age 49, 87% M (included 18 patients >70 g alcohol/day defined as ARLD)	5.4	US	Questionnaire at baseline and every 6 months	g/day in categories with <20 g/day as reference	HCC on imaging	Age, sex, BMI, T2DM, serum markers	g/day alcohol versus <20 g/day 20–39 hour 0.90 (0.11 to 7.90) p=0.919 ≥40–69 hour 2.48 (1.01 to 6.05) p=0.047 >70 hour 12.61 (5.68 to 28.00) p=0.001	Low

*Note multiple differences in means and OR presented for different histological and biochemical outcomes between abstainers, persistent moderate drinkers, and changes in alcohol consumption between biopsies. Presented data represent histological outcomes of potential clinical prognostic significance within the remit of this review comparing persistent moderate drinking to abstinence.
†Multiple HR presented in paper for different score outcomes for single and repeated outcome measures looking at intermediate/high or high-risk scores in low and moderate drinkers and different subgroups. Presented data represent outcomes best in keeping with remit of this review using widely used indirect serum markers of liver fibrosis.
‡Scores used to estimate fibrosis progression were the Fib4 score, NAFLD fibrosis score (NFS) and AST to platelet ratio index (APRI) score.
ARLD, alcohol-related liver disease; AUDIT-C, alcohol use disorders identification test - consumption; BMI, bodymass index; BP, blood pressure; CRN, clinical research network; FINRISK, Finland cardiovascular risk study; FLI, Fatty Liver Index; g, grams; HCC, hepatocellular carcinoma; M, Male; NAFLD, non-alcohol-related fatty liver disease; NASH, non-alcohol related steatohepatitis; RF, risk factor; T2DM, type 2 diabetes mellitus; US, hepatic ultrasound; Yrs, years.

progression to advanced liver fibrosis using non-invasive blood-based markers of disease. For moderate drinkers (10–30 g/day), the risk of progressing to advanced fibrosis (using intermediate/high Fib4 score as the outcome) was HR 1.33 (1.13 to 1.57), when compared with abstainers. Light drinkers (1–10 g/day) showed a tendency towards more advanced disease when compared with abstainers, but this did not reach statistical significance (HR 1.08 CI 0.91 to 1.27).

Moderate alcohol consumption (below the threshold that would be consistent with ARLD) and risk of liver disease progression in NAFLD

Three studies extended the definition of moderate alcohol consumption beyond the international consensus definition of moderate consumption. Two of the studies were rated as having a low risk of bias,[57 61] with one rated as high risk of bias.[56]

The general population longitudinal data presented by Chang *et al*[59] is supplemented by two recent related studies by Åberg *et al*,[56 57] using data from the same Finnish National Health Surveys (FINRISK, Health 2000) cohort. The definition of moderate alcohol consumption was increased to include anything up to 50 g/day in these studies. Although the exposures and outcome measures were the same in the two related studies, the NAFLD population was defined using different Fatty Liver Index (FLI) cut offs values, generating overlapping but distinct study populations. For this reason, data are presented from both studies.

The first study, only available as a conference abstract,[56] used a FLI>30 to retrospectively define their NAFLD population. This low FLI would generally be used as a 'rule out' rather than 'rule in' cut-off for NAFLD diagnosis[62] and the limited data presented suggests that using abstinence as a reference, any increase in alcohol consumption by 10 g/day, increased incident liver events (combined fatal and non-fatal outcomes) by 43% with a presented HR of 1.43 (1.12 to 1.82) for each 10 g rise in daily alcohol consumption. The data presented contained few details of adjustment factors or analysis plan. This study was graded as having a high risk of bias, and these results should be interpreted with caution.

A larger study,[57] based on the same cohort, retrospectively identified a NAFLD population based on a FLI of >60 (the accepted and validated cut-off for making a positive diagnosis of NAFLD in the literature[63]). Alcohol intake at cohort entry was based on estimated consumption over the previous year. Lifetime abstainers were used as the reference group. Fatal and non-fatal liver outcomes were studied in 8345 participants over 92 350 person years of follow-up. The study concluded that incident liver disease is higher at all levels of alcohol consumption, compared with lifetime abstainers with steadily rising HRs as the level of alcohol consumption increases. Although drinking up to 10 g/day was not statistically significantly different to abstaining (HR 1.38 CI 0.74 to 2.58 in the final model), levels of alcohol consumption between 10 g and 19 g, which are roughly equivalent to the 14 units per week recommended limits, prognosticated for over double the number of incident liver events in NAFLD patients (HR 2.18 CI 1.05 to 4.53). At higher levels, which would not necessarily trigger a liver assessment for alcohol related harm in current guidelines, risk of significant liver disease was nearly nine times higher (for consumption of 40–49 g of alcohol a day, HR 8.79 CI 3.95 to 19.56).

A retrospective Japanese cohort study[61] also looked at stepwise rises in daily alcohol consumption as a prognostic factor for the more specific outcome of hepatocellular carcinoma (HCC) in people with fatty liver (identified on ultrasound). The Kawamura study with 9959 participants followed for a median of nearly 2000 days, had a reference group of people drinking <20 g of alcohol per day, rather than abstainers. This differed from all the other studies reviewed. Only those drinking at between 40 and 69 g of alcohol a day had a statistically significant increase in rates of HCC (HR 2.48 CI 1.01 to 6.05, p 0.047), with no effect in those drinking at more moderate levels. The population in this retrospective cohort were patients undergoing ultrasound at two tertiary hepatology centres in Japan rather than a general population cohort, and as HCC is known to occur in non-cirrhotic NAFLD[64] comparison with outcomes from other studies should be interpreted with caution.

Excluding the only study rated as having a high risk of bias,[56] the other good quality longitudinal studies of varying design, all reported either no association or a negative impact of moderate amounts of alcohol on future liver disease outcomes. This was seen across the studies looking at levels of alcohol consumption within the international definition of moderate consumption, and those that extended this definition of moderate consumption.

DISCUSSION

Summary of results

In this systematic review of the latest available longitudinal data, we found evidence to suggest that any amount of alcohol, even at low levels, may be harmful for liver health in people with diagnosed NAFLD. This evidence comes from both general population-based cohorts using coded liver outcomes, as well as tertiary centre NAFLD populations defined using histological end points.

Comparison with existing literature

Until recently the majority of evidence in this area has come from cross-sectional studies where alcohol exposure was assessed at the same time as liver outcomes. These data provide somewhat contradictory results, with several studies indicating that moderate alcohol consumption is associated with lower levels of liver disease progression[39 43 65 66] although more recent studies support of our findings, and suggest the opposite.[42 45] The design employed in these studies does not allow the assessment of temporal relationships and is open to reverse causality

(those with liver damage may be newly abstaining from alcohol for example) in addition to recall and other biases. On the basis of these limitations, cross-sectional studies were excluded from this current review, although they have been widely cited in previous critical reviews in this area, before more recent longitudinal data were available.

In the historical absence of large prospective cohort studies and the impossibility of conducting a controlled trial in the area, comparative work has been undertaken using Mendelian randomisation. This utilises random genetic variations which affects the rate of alcohol metabolism as a proxy measure for alcohol exposure, with randomisation of patients with NAFLD based on an allele known to confer lower lifetime alcohol consumption by necessity due to the unpleasant effects of drinking even low levels of alcohol. Findings from this study were supportive of our review, with the group with higher lifetime alcohol consumption showing markers of more severe disease on biopsy, even though alcohol consumption was at very modest levels.[46]

In addition to the evidence on the relationship between modest alcohol consumption in NAFLD and liver outcomes, other published studies have focused on overall mortality and cardiovascular outcomes. A study of 4264 participants in an ultrasound diagnosed NAFLD cohort study showed no significant difference in overall mortality in those with alcohol consumption in the low/moderate range versus abstinence after 20 years of follow-up.[36] A subsequent study with the same US cohort reported a protective effect of low alcohol consumption on overall survival in NAFLD.[67] The evidence for a protective effect of low alcohol consumption on cardiovascular outcomes in the general population is generally accepted.[68] The evidence for cardiovascular protection in those with NAFLD is more limited, with some evidence that moderate alcohol may provide some benefit[69] but more recent studies finding no protective effects.[42 70] The comparative evidence on overall mortality and cardiovascular outcomes highlights the need to assess liver disease risks within these competing contexts.

Strengths and limitations

Although there have been several recent critical reviews of the role of moderate alcohol consumption in NAFLD, the most recent of which reach similar conclusions,[4 49 71] these have been wider in their remit with less well-defined inclusion criteria and less systematic methodology. The predetermined inclusion criteria, robust systematic data collection and reporting techniques (in line with PRISMA guidelines) and decision to avoid cross-sectional data are all important in providing the best available evidence to answer the review question of the temporal relationship between moderate alcohol consumption and liver outcomes in NAFLD. The challenges of synthesising observational data, including unmeasured confounding and heterogeneity, were anticipated, but meant that data pooling was not possible.

A particular limitation hindering comparison between studies was the methods of defining moderate alcohol consumption. The consensus for defining a level of alcohol consumption above which a diagnosis of pure NAFLD cannot be made have been supported by the European Association for the Study of the Liver and the American Association for the Study of the Liver Diseases and set at 20 g/day in women and 30 g/day in men,[62 72] yet most of the published studies do not use these cut-offs in their data. Until this is standardised across studies, with an additional consensus defining levels above this moderate but not high enough to reach levels associated with a definite diagnosis of ARLD, synthesising the evidence in this area will remain challenging.

Implications for research/practice

This review adds weight to individual studies showing that any level of alcohol intake in NAFLD may be harmful to liver health. Further prospective cohort studies are needed, with detailed definitions/measures of alcohol exposure, and validated clinical liver outcomes, measured at appropriate times. Future research should focus on looking at outcomes in relation to accepted alcohol intake levels used in definitions of NAFLD. It should also take into account that the clinical reality is a dual-aetiology patient who may currently be excluded from both diagnostic categories based on their alcohol intake being too high for NAFLD, and too low for ARLD definitions. This is an ever-expanding patient group seen in many clinical settings.

Based on a synthesis of the evidence presented in this review, clinicians seeing patients with NAFLD in primary or secondary care should currently advise abstinence from alcohol to avoid accelerating liver harm. This is likely to be difficult for patients to accept, and public health messaging will need careful thought if it is to have any impact on liver health.

Contributors HJ: conceptualisation, methodology, conduct, analysis, writing of initial draft, guarantor. HO'K: methodology, conduct, figures/infographic, critical review and comments on drafts. DC: supervision of methodology, conduct, critical review and comments on drafts. DS: methodology, conduct, critical review and comments on drafts. BH: conceptualisation, supervision of methodology, conduct, analysis, critical review andcomments on drafts. QMA: conceptualisation, supervision of conduct and analysis, critical review and comments on drafts.

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Patient consent for publication Not applicable.

Ethics approval This study does not involve human participants.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

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Medline(Ovid)

1. (((fatty or fat or steato*) adj3 (liver* or hepat*)) or steatohepat* or (visceral adj2 steato*)).ti,ab.
2. non-alcoholic fatty liver disease/
3. fatty liver/
4. (nafl* or nash).ti,ab.
5. non?alcoholic steato*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
6. (non?alcoholic adj3 (liver or fat*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
7. or/1-6
8. exp Alcohol Drinking/
9. Alcoholism/ or Alcoholic Beverages/
10. (alcohol adj2 (unit* or consum* or level* or mg or g)).ti,ab.
11. (moderat* adj3 alcohol*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
12. or/8-11
13. 7 and 12
14. liver disease.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
15. fibrosis.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
16. (scar* adj3 liver).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
17. cicatrix.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
18. (end-stage adj3 liver).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
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20. (hepatic insufficiency or liver failure or end stage liver disease or hepatic failure or hepatic encephalopathy or hepatic impairment).mp. [mp=title, abstract, original title, name of substance

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word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
21. (mortality or death or dead or deceased or passed away).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
22. ((hepatocellular or liver cell) adj carcinoma).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
23. or/14-22
24. 13 and 23
25. limit 24 to yr="1990-Current"

Embase(Ovid)

1. (((fatty or fat or steato*) adj3 (liver* or hepat*)) or steatohepat* or (visceral adj2 steato*)).ti,ab.
2. exp nonalcoholic fatty liver/
3. (nafl* or nash).ti,ab.
4. non?alcoholic steato*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
5. (non?alcoholic adj3 (liver or fat*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
6. or/1-5
7. drinking behavior/
8. exp alcoholism/
9. exp alcoholic beverage/
10. (alcohol adj2 (unit* or consum* or level* or mg or g)).ti,ab.
11. (moderat* adj3 alcohol*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
12. or/7-11
13. 6 and 12
14. liver disease.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
15. fibrosis.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
16. (scar* adj3 liver).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
17. cicatrix.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

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19. (end-stage adj3 liver).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
20. (Mortality or death or dead or deceased or passed away).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
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22. (hepatic insufficiency or liver failure or end stage liver disease or hepatic failure or hepatic encephalopathy or hepatic impairment).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
23. or/14-22
24. 13 and 23
25.
26. limit 25 to yr="1990 -Current"

Cochrane library

ID Search Hits
#1 (((fatty or fat or steato*) NEAR/3 (liver* or hepat*)) or steatohepat* or (visceral NEAR/2 steato*))
#2 MeSH descriptor: [Non-alcoholic Fatty Liver Disease] this term only
#3 MeSH descriptor: [Fatty Liver] this term only
#4 (nafl* or nash)
#5 non?alcoholic steato*
#6 (non?alcoholic NEAR/3 (liver or fat*))
#7 #1 or #2 or #3 or #4 or #5 or #6
#8 MeSH descriptor: [Alcohol Drinking] explode all trees
#9 MeSH descriptor: [Alcoholism] this term only
#10 MeSH descriptor: [Alcoholic Beverages] this term only
#11 (alcohol NEAR/2 (unit* or consum* or level* or mg or g))
#12 (moderat* NEAR/3 alcohol)
#13 #8 or #9 or #10 or #11 or #12
#14 #7 AND #13
#15 Liver disease
#16 Fibrosis
#17 cicatrix or (scar* NEAR/3 liver)
#18 (end-stage NEAR/3 liver)
#19 ((Liver or biliary) NEAR cirrhosis)
#20 (hepatic insufficiency or liver failure or end stage liver disease or hepatic failure or hepatic encephalopathy or hepatic impairment)
#21 (Mortality or death or dead or deceased or passed away)
#22 ((hepatocellular or liver cell) NEAR carcinoma)
#23 #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22

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#24 #14 AND #23 with Cochrane Library publication date Between Jan 1990 and Dec 2019

CINAHL(EBSCO)

S1 TI ((((fatty or fat or steato*) N3 (liver* or hepat*)) or steatohepat* or (visceral N2 steato*))) OR AB ((((fatty or fat or steato*) N3 (liver* or hepat*)) or steatohepat* or (visceral N2 steato*))) OR (MH "Nonalcoholic Fatty Liver Disease") OR (MH "Fatty Liver") OR TI ((nafl* or nash)) OR AB ((nafl* or nash)) OR non#alcoholic steato* OR ((non-alcoholic N3 (liver or fat*)))
S2 (MH "Alcoholic Drinking+") OR (((MH "Alcoholism") or (MH "Alcoholic Beverages"))) OR TI ((alcohol N2 (unit* or consum* or level* or mg or g))) OR AB ((alcohol N2 (unit* or consum* or level* or mg or g))) OR AB (moderat* N3 alcohol)
S3 S1 AND S2
S4 (Liver Diseases OR Liver Failure OR ((Liver or biliary) N1 Cirrhosis) OR Fibrosis OR Cicatrix OR (scar* N3 liver) OR (end-stage N3 liver) OR hepatic insufficiency OR end stage liver disease OR hepatic failure OR hepatic encephalopathy OR hepatic impairment OR Mortality OR death OR dead OR deceased OR passed away OR ((Hepatocellular OR liver cell) N1 carcinoma))
S5 S3 AND S4

Web of Science (CPCI)

1. TS = (((fatty or fat or steato*_ NEAR/3 (liver* or hepat*)) or steatohepat* or (visceral NEAR/2 steato*))
2. TS = non-alcoholic fatty liver disease
3. TS = fatty liver
4. TS = (nafl* or nash)
5. TS = non-alochol steato*
6. TS = (non-alcoholic NEAR/3 (liver or fat*))
7. #1 OR #2 OR #3 OR #4 OR #5 OR #6
8. TS = alcohol drinking
9. TS = (alcoholism or alcoholic beverages)
10. TS = (alcohol NEAR/2 (unit* or consum* or level* or mg or g))
11. TS = (moderate NEAR/3 alcohol*)
12. #8 OR #9 OR #10 OR #11
13. #7 AND #12
14. TS = liver disease
15. TS = fibrosis
16. TS = cicatrix
17. TS = (end-stage NEAR/3 liver)
18. TS = liver cirrhosis
19. TS = hepatic insufficiency
20. #14 OR #15 OR #16 OR #17 OR #18 OR #19
21. #13 AND #20

2.3.1 PP2 commentary

There remains, in the research and literature, a false dichotomy between ALD and MASLD. It is increasingly common for people who drink alcohol at harmful levels to also be overweight and have type 2 diabetes or other metabolic risk factors. It is well known that the group with very high alcohol consumption increase their chances of poor liver outcome even further if they do have metabolic co-morbidity or obesity (66-68). This systematic review presents the most up to date evidence from longitudinal studies. We found that the reverse is true - in people with diagnosed MASLD any level of alcohol consumption may be harmful and there is no evidence in this group that low levels of alcohol consumption have a protective effect on liver health. This evidence must be considered in the context of competing risk/benefits, and must be cognizant of the established evidence that low levels of alcohol consumption have some protective effect on cardiovascular outcomes (69,70). The findings of this review would support advice on abstinence from alcohol for people with MASLD, to avoid accelerating liver harm.

Since the publication of this review the new nomenclature consensus allows for recognition of this group with dual pathology under the steatotic liver disease (SLD) umbrella with a new term MetALD to reflect the common occurrence of these overlapping risk factor (16) and a need for further research in this group.

2.4 Chapter summary

Risk factors that may put people at risk of significant liver disease outcomes are well established for ALD, viral hepatitis and rarer causes of liver disease. MASLD is extremely common with around a third of the UK adult population likely to have some degree of fatty liver as a result of metabolic risk factors (4). Significant liver disease (cirrhosis or liver mortality) resulting from MASLD is much less common. In general practice better definition of the important risk factors would allow clinicians to focus liver

assessments, referral and targeted interventions on people most likely to benefit. An initial focus on people with diabetes, and those with MASLD who also drink moderate or high levels of alcohol, is a sensible initial approach to tackling this high prevalence, low severity condition.

Chapter 3: Current pathways of care in the community for chronic liver disease in the UK

My previous chapters have contributed to the definition of people at risk of liver disease in the general population. This chapter adds to the evidence on the availability of pathways of care for people at risk of liver disease, as defined by known risk factors or abnormal liver blood tests. The first publication presented in this chapter provides a critical analysis of current research into clinical pathways of care, discussing the advantages and disadvantages of some of these different approaches. The second publication presents a survey carried out in collaboration with the British Liver Trust, highlighting the varied national picture around population access to pathways of care for those at risk of, and with, liver disease. It was essential to define the current situation and highlight inequities in care before moving on to research improved design and implementation of pathways of care for liver disease.

3.1 What are the current approaches to community liver disease pathways?

3.1.1 Entry points into and tests employed within pathways of care

The majority of research in the area of community pathways of care for liver disease has focused on the content: Which group should have tests? Which tests should be done? What should be the test cut-offs, used to trigger a secondary care referral, and what order and sequence should the tests be done in? We have already presented some additional data to guide the first of these questions in low prevalence population settings in chapter 2.

The last twenty years has seen an explosion in the development and interest in better tests to find early liver disease. The correlation between basic liver blood test abnormalities and level of structural damage to the liver is known to be poor, with UK

studies noting that a majority of patients having abnormal liver blood tests in primary care do not go on to have a diagnosis of liver disease made (21). This has led to a nomenclature change, with the latest national guidelines referring to these basic tests, commonly carried out in primary care, as ‘liver blood tests’ rather than the previously used ‘liver function tests’ (22), reflecting their inability to tell us in isolation about the functioning of the liver. In response to this need, several non-invasive liver tests (NITs) have been developed and validated to look for fibrosis of the liver (mainly using secondary care patients with biopsy proven liver disease) (71-73). These NITs include the indirect serum markers (combinations of routine tests/patient demographics used in formulae to develop scores to predict likelihood of liver damage e.g the commonly used Fib4 score (74), and direct serum markers which measure combinations of substances released directly from the damaged liver. NITs also include imaging modalities, in particular vibration controlled transient elastography (VCTE, marketed as Fibroscan™, Echosens, France) which directly measures liver stiffness as a marker of liver fibrosis/cirrhosis. The diagnostic accuracy of these NITs mentioned above, in addition to other more specialised and recently developed biomarkers, has been analysed in large cohorts of patients with biopsy proven MASLD (75), but there is more limited evidence of accuracy and use in general population cohorts.

It is beyond the scope of this thesis to go into the detail of the development and validation of all of these tests but I include a table (Table 1) summarising some of the common NITs available in the community setting. These are referred to in the presented papers.

Table 1: A summary of non-invasive liver tests (NIT) available in primary care practice.

Test:	Category:	Detail of test:	Availability in primary care:	Reference to development/ use:
Fib4 score	Indirect serum marker	AST, ALT, platelet count, age in formula	all	Sterling RK et al 2006 (76)

NAFLD fibrosis score	Indirect serum marker	Age, BMI, diabetes, AST, ALT, platelet count, albumin in formula	all	Angulo P et al 2007 (77)
AST:ALT ratio	Indirect serum marker	AST:ALT expressed as ratio	all	Giannini E et al 1999 (78)
Enhanced Liver Fibrosis (ELF) test	Direct serum marker	hyaluronic acid (HA),procollagen III amino-terminal peptide (PIIINP), tissue inhibitor of matrix metalloproteinase 1 (TIMP-1) in formula	limited	Day J et al 2019 (79)
VCTE (Fibroscan)	Imaging modality	Stiffness measurement (Kpa) directly related to shear wave velocity using US probe	limited	Castera L et al 2008 (80)

The indirect serum markers all have very good and comparable negative predictive values (73), but have been criticised for the numbers of false positive results, particularly when used in general population low prevalence settings (81). The only direct marker currently available in UK primary care is the Enhanced Liver Fibrosis (ELF™, Siemens Heathaneers, USA) test (71). Utilising ELF in population settings is likely to result in fewer false positive tests (81), but is more expensive and requires the pathology labs to buy in specialised equipment under patent. It has also been criticised for the lack of data around its performance and the validity of values triggering referrals in the primary care setting (82). Fibroscan™ has advantages of better positive predictive values and the ability to give a patient an immediate result which can be combined with a behavioural intervention (41) . Although the use of Fibroscan™ in the community setting has recently been recommended by NICE (83), it requires a room, machine and operator and for population level case finding, some argue little benefit over the use of the ELF test which is a simple blood test (81). Although there are still active research

studies ongoing to elucidate the best tests and combinations to use to assess for liver damage in the community setting (50,84), there is general agreement that effective pathways are likely to involve a two step pathway based on employing simple, cheap tests initially, with ELF and/or Fibroscan™ being used as a second step.

3.1.2 Availability of pathways of care across the UK

Pathways using these varied testing approaches have been researched and implemented. A recent (after the publications presented in this chapter were completed) systematic review of these community pathways revealed UK predominance in developing these pathways of care (note publication searches were limited to the English language) (85). As well as highlighting the variety of approaches taken in terms of NITs and test cut-offs used, the review also highlighted differences in approaches from stand-alone liver pathways utilising research funding/specialist nursing teams (86) to commissioned quality improvement projects integrated into existing long term conditions management (87). It has been acknowledged that not all collaborations between health care commissioners and providers of care for people with liver disease will have been published as research, hence the rationale for a national survey to gauge the availability of community pathways for the management of liver disease.

3.2 PP3 The pathway to better primary care for chronic liver disease

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Analysis

The pathway to better primary care for chronic liver disease

THE INCREASING HEALTH BURDEN OF LIVER DISEASE: A CASE FOR A CHANGE IN APPROACH

Liver disease, most commonly caused by alcohol or the metabolic syndrome (leading to non-alcohol related fatty liver disease [NAFLD]), is now a leading cause of premature death in the UK.[1] Morbidity and mortality due to liver disease have been rising in line with obesity, diabetes, and high levels of hazardous alcohol consumption. Liver disease caused by chronic viral hepatitis is an exception to this trend, with successful vaccination programmes for hepatitis B, along with very effective curative treatments for hepatitis C, leading to a reduction in end-stage liver disease as a result of these aetiologies in the UK.[2] Most patients with cirrhosis are diagnosed late, with up to 70% presenting with a complication of cirrhosis, such as variceal haemorrhage or ascites.[3] Rising mortality rates due to liver disease are in sharp contrast to most other chronic diseases in the UK, where rates have been steadily falling with improved primary and secondary prevention, and better access to effective interventions.[3] This has been partly driven by enhanced risk assessment and early intervention in primary care.[4]

Liver disease should now be considered as a preventable chronic disease. Risk factors are well known and easily identifiable, and access to diagnostic tests and evidence-based interventions has improved. But adoption of a preventive approach in primary care will require a major shift in the framing of liver disease. GPs are more familiar with reacting to abnormal blood results or a late-stage decompensated cirrhotic patient. In contrast with the preventive approach widely adopted for conditions such as heart disease, proactive assessment of the patient with risk factors for liver disease has not yet been widely accepted. There are no Quality and Outcomes Framework (QoF) incentives or widely followed guidelines in UK general practice to prompt change, although evidence is mounting that this would be a clinical and cost-effective response to rising levels of disease and death.

RESPONDING TO THIS INCREASED DISEASE BURDEN: POLICY INITIATIVES, GUIDELINES, AND RESEARCH

The rising burden of liver disease and the obvious disparity between liver disease and other chronic disease outcomes has led to a number of recent policy initiatives. A *Lancet* commission addressing liver disease in the UK was established in 2014 inviting a broad range of clinical, public health, and policy experts to establish a blueprint for improving liver disease outcomes.[3] Initial recommendations and subsequent updates have all focused on improving the detection of liver disease in primary care as a priority goal.[5] The Royal College of General Practitioners (RCGP), in collaboration with the British Liver Trust, made liver disease a priority area from 2016–2019. In addition to developing online clinical management resources,[6] the partnership led to the publication of commissioning recommendations. This recognised that a policy approach was required to change individual practice.[7] Lobbying by these groups has led to a recent change in the NHS Health Check best-practice guidelines, with a clinical assessment for liver damage now recommended for individuals reporting a history of hazardous alcohol consumption.[8] These policy initiatives could have gone further with a more proactive approach to liver assessments for people with NAFLD risk factors, but the evidence base fell short of being able to support this. The latest National Institute for Health and Care Excellence (NICE) guidelines on NAFLD and liver cirrhosis were both published in 2016[9,10] and already need updating with the rapid expansion of relevant research in the area.

Much recent research has focused on the clinical utility and cost-effectiveness of novel approaches to finding liver disease in the community, using primary care pathways. Three important areas have been identified: a structured or automated approach to the interpretation of liver blood tests; a more proactive approach to identifying who may be at high risk of significant liver disease; and improved community access to better diagnostic tests. It is likely that a comprehensive strategy to tackle early liver disease would have to incorporate all three of these approaches, and much of the published work in this area now recognises this.

> *"Liver disease should now be considered as a preventable chronic disease. Risk factors are well known and easily identifiable, and access to diagnostic tests and evidence-based interventions has improved."*

THE INTERPRETATION OF LIVER BLOOD TESTS: MOVING TOWARDS TARGETED TESTING AND AUTOMATION

Large numbers of liver blood tests are requested every day in primary care, as part of diagnostic work-up and treatment monitoring. A high proportion of these tests report at least one liver blood test abnormality and many of the abnormal tests are never investigated any further.[11,12] A large UK study concluded that the majority of people in primary care with abnormal liver blood tests, but no clinical suspicion of liver disease, did not have diagnosed liver disease when actively investigated.[13] This highlights the importance of the initial decision to request these tests, which should be based on clinical suspicion arising from knowledge of risk factors, or for specific drug monitoring, with agreed thresholds for drug discontinuation. How to respond to a mildly abnormal test outside of these contexts is the more difficult question. Targeted initial testing will reduce the proportion of 'unexpected' abnormal results and allow time and resources to focus on people at higher risk of clinically significant liver disease.

In part because of the reasons outlined above, GPs find the area of interpretation of liver blood tests challenging and many of the published algorithms are complex.[14] In recognition of this, the British Society of Gastroenterology, in collaboration with a wide panel of stakeholders, developed a comprehensive guide to the management of abnormal liver blood tests, which advocates for early decision making around risk factors and likely aetiology, to avoid repeat testing.[15] Creation of an 'intelligent' liver blood test requesting and

"Comprehensive uptake of a standardised approach to chronic liver disease management in UK primary care remains elusive."

reporting system takes these guidelines a step further, and has been developed and implemented in Tayside, Scotland.[16] Using existing IT pathology systems, the requestor inputs some basic information about the patient including alcohol intake, metabolic risk profile, and test reason. The test is then processed by the lab in the context of this information with additional further second-line tests being analysed automatically according to initial results. Rather than isolated results being fed back, a complete results panel is produced with a suggested likely cause for the abnormality and advice on further management. This has led to a significant reduction in the number of abnormal liver tests that have not been appropriately investigated and managed.[16]

NOVEL PATHWAYS FOR MANAGING COMMON CAUSES OF CHRONIC LIVER DISEASE IN THE COMMUNITY

As the commonest reasons for liver blood abnormalities in primary care are alcohol-related liver disease (ARLD) and NAFLD, several collaborative groups have developed referral pathways for these conditions. The pathways aim to identify the minority who are at a high risk of developing liver cirrhosis, to refer them on for specialist management. The majority are directed to community-based management, with a focus on lifestyle modification and addressing risk factors in the context of multimorbidity and holistic care. The Camden and Islington Pathway is a recently published example of this approach, which focuses on liver fibrosis assessment for people presumed to have NAFLD.[17] A clinical commissioning group (CCG)-wide approach was studied, where individuals with abnormal liver blood tests from presumed NAFLD had liver fibrosis staging using a two-step process in primary care. An initial assessment of the likelihood of significant liver disease was carried out using a Fib-4 score, which uses a combination of routinely available blood tests in an algorithm giving a likelihood score for advanced liver fibrosis. Patients identified as low risk of progressive liver disease using the Fib-4 score could then be confidently managed by primary care with guidance to recheck the Fib-4 score every 3 years. If this test showed patients to be in an 'indeterminate category' this was followed by the NICE-recommended enhanced liver fibrosis (ELF) test (a direct liver fibrosis serum marker) before a referral decision was made. Direct referral was recommended in those with a high-risk Fib-4 score. This more structured approach with increased test availability led to a three-fold increase in cirrhosis detection, and reduced unnecessary referrals (where no liver fibrosis was detected) by 80%.[17] Other CCGs have commissioned similar pathways. The inclusion of patients with ARLD and the addition of GP direct access to transient elastography (FibroScan) have led to large increases in the detection of advanced fibrosis/cirrhosis in these published examples.[18]

Reliance on abnormal liver blood tests alone to enter a detection pathway will miss a significant proportion of individuals with advanced liver disease. Liver blood tests are insensitive for the detection of advanced liver disease secondary to NAFLD and ARLD. In order to increase the early detection of significant liver disease, alternative approaches using liver disease risk factors to trigger an assessment have been studied. A good example of this approach is the Nottingham Scarred Liver Project, which has become a regionally commissioned pathway following a successful pilot project.[19] In this pathway, individuals with risk factors including type 2 diabetes, obesity (BMI >30), the metabolic syndrome, or harmful alcohol use are triaged directly to have transient elastography conducted regardless of any abnormality in liver enzymes. This risk-based approach found that 6% of those with these risk factors who underwent transient elastography had cirrhosis. If these patients had been triaged using abnormal liver blood tests alone, 39% of these cirrhosis cases would have been missed.[19] Both the Scarred Liver Project and Camden/Islington approach have been shown to be highly cost-effective as compared with standard care.[20,21]

WHAT NEXT FOR CHRONIC LIVER DISEASE MANAGEMENT IN PRIMARY CARE?

Comprehensive uptake of a standardised approach to chronic liver disease management in UK primary care remains elusive. This is despite the existence of recently updated guidelines and commissioning recommendations, more automated approaches, and better access to improved diagnostic tests and pathways. There are many potential reasons for this, including a historical lack of emphasis on liver disease in the GP training curriculum contributing to low confidence in this area of practice.[14] As part of the RCGP liver disease priority work from 2016–2019 the curriculum has now been updated to reflect the importance of increasing liver disease morbidity and mortality as an emerging issue.[22] Liver disease outcomes have been consistently absent from the QoF and it is hoped that the introduction of new quality improvement (QI) modules as part of the QoF may provide a long overdue opportunity to prioritise improvements in liver disease outcomes at a primary care level. There is still a pervasive attitude that diagnosing liver fibrosis and cirrhosis is futile, as therapeutic options are limited to 'only lifestyle interventions'. As well as mounting evidence for the effectiveness of these lifestyle interventions in both ARLD and NAFLD,[23,24] there are also now a number of drugs in late-stage clinical trials shown to be effective in slowing liver fibrosis/progression to cirrhosis.[25] Finally, there remains an absence of implementation research into liver disease pathways and how these may fit into the many competing priorities within high primary care workloads.

Tackling the challenges of implementing new chronic disease management pathways in primary care, and how liver disease

"Tackling the challenges of implementing new chronic disease management pathways in primary care, and how liver disease fits into established ways of working, is key to improving ... effectiveness."

fits into established ways of working, is key to improving usability and therefore effectiveness. An inclusive approach to pathway development is crucial to maximise clinical impact, while minimising any additional workload. Primary care professionals and service users will need to be at the core of any change. GPs are already working at more than full capacity and approaches that are funded and dovetail with established and related management pathways (for example, diabetes and obesity management) are most likely to be implementable outside of a research environment. Any future research into this area must consider real-world implementation throughout the research process, as well as further defining the best clinical approach incorporating risk assessment, optimal use of diagnostic modalities, and referral criteria/intersectional working.

The pathway to better primary care for chronic liver disease is becoming clearer: if primary care is serious about improving outcomes for patients with liver disease, now is the time to implement change.

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3.2.1 PP3 commentary

In this analysis paper we set out the current approaches and challenges to implementing pathways of care for liver disease in primary care. Current approaches, including better structures and more automated approaches to interpretation of liver blood tests, proactive approaches to identifying significant liver diseases on the basis of risk factors and improved community access to better diagnostic tests, must all go hand in hand. Inclusion of primary care and patient/public leadership in developing these current strategies has been lacking to date as well as the consideration of implementation outcomes alongside clinical and cost-effectiveness in the limited research environment.

3.3 PP4 Engagement with community liver disease management across the UK: a cross-sectional survey

Jarvis H, Worsfold J, Hebditch V, Ryder S. BJGP Open. 2021 Jul 5; BJGPO.2021.0085. (47)

BJGP Open

RESEARCH

Engagement with community liver disease management across the UK: a cross-sectional survey

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Abstract

Background: Liver disease is an increasing cause of premature mortality in the UK. Its management in primary care is not well understood. It is unclear what role commissioning bodies are playing in liver disease in the UK.

Aim: To assess the level of engagement with community chronic liver disease management among clinical commissioning groups (CCGs) and health authorities across the UK.

Design & setting: A cross-sectional survey to all UK CCGs and health authorities.

Method: Survey questions were developed by the British Liver Trust, in collaboration with topic experts, and evaluated structures in place relating to liver disease management at commissioning and health board level.

Results: There were 159 responses representing 99% UK coverage of CCGs and health boards. Twenty per cent reported an individual responsible for liver disease within their organisation, with 40% and 29% reporting having pathways in place to respond to abnormal liver blood tests and liver disease more generally, respectively. All those reporting use of pathways reported using national guidelines to guide content. Twenty-five per cent made use of transient elastography (FibroScan) and 16% of direct serum fibrosis markers (for example, enhanced liver fibrosis [ELF] score), which are both part of current National Institute for Health and Care Excellence (NICE) guidelines. There was marked regional variation in all areas of engagement surveyed, with Wales having exceptionally high levels of engagement in all areas in contrast to the other nations.

Conclusion: The results of this survey should be used as a catalyst to highlight necessary regional improvements to the primary care management of chronic liver disease across the UK.

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How this fits in

Liver disease morbidity and mortality is increasing in the UK. GPs report a gap in knowledge and confidence in managing liver disease and it is unknown how commissioners are engaging with liver disease management. This study reports that commissioner or health board engagement with chronic liver disease shows unacceptable variation across the UK. The results should be used by clinicians and policymakers to improve primary care management of liver disease and reduce inequalities in care.

Introduction

Liver disease is a common and increasing cause of morbidity and premature mortality in the UK and globally.[1] This is in contrast to other common chronic diseases such as heart disease where reduction

in morbidity and mortality has been seen over the past 50 years.[2] The main causes of liver disease in the UK are alcohol-related liver disease (ARLD) and non-alcohol-related fatty liver disease (NAFLD), which is increasing in parallel with the obesity and type two diabetes mellitus (T2DM) epidemics seen in the UK and across the globe.[3] As such, the risk factors for liver disease are in common with those for many other chronic diseases and cancers.

Chronic disease management is one of the cornerstones of primary care work, with management pathways, as well as diagnostic and treatment services, available locally and often incentivised nationally in the UK.[4] This has led to more standardised evidence-based care for people living with T2DM, heart disease, and a range of other chronic conditions. At a practice level, this has led to widespread use of protocols and templates, with primary care nursing teams often being able to competently take the lead in chronic disease management along with high confidence and knowledge in these areas of clinical practice.[5,6]

Health care is organised differently in the four nations of the UK. England has CCGs, with the devolved nations maintaining the health board or authority model. These organisations fulfil a similar regulatory and oversight function for their population and support this effective community management of chronic disease, with disease or system-specific clinical leads to drive decisionmaking around diagnostics, referral pathways, and community interventions to standardise evidence-based care.

In sharp contrast to other disease areas, many GPs report a gap in confidence and knowledge when it comes to managing chronic liver disease.[7] It is unclear if national guidelines,[8,9] diagnostic tests, and exemplar pathways[10,11] have become normalised and part of general practice in liver disease management across the UK. There is a notable lack of incentivisation for managing liver disease as a chronic disease across most of the UK, with no current or historical Quality and Outcome Framework (QOF) targets for liver disease.[12]

The aim of this study was, therefore, to assess the levels of engagement with chronic liver disease management among primary care commissioning bodies and health authorities across the UK. The primary objectives were first to ascertain whether structures and named decisionmakers were in place specific to liver disease management, and second whether guidelines were being promoted, including the evidence-based use of nationally recommended diagnostic tools.

Method

An online cross-sectional survey was sent out to all UK commissioning bodies and health authorities between June and October 2020. All English CCGs and devolved nation equivalent health boards were included as participants in the study if a named contact could be identified from publicly available listings.

Questions in the survey evaluated structures and processes in place relating to liver disease detection and management at commissioning or health board level. The full survey content is available in Supplementary file 2. The survey was sense-checked on a small number of recipients before wider rollout. Owing to the initial low response rate, further responses were obtained using a freedom of information request (or equivalents in the devolved nations). At this stage responders were given the choice to respond to the online survey or fill in their responses on a Word document version of the survey.

Responses were collated from both collection methods and entered onto a Microsoft Excel spreadsheet by JW (checked by HJ) for analysis. A sample of the responses (n = 15/159, 9.4%) was cross-checked by direct contact with liver specialists in hospitals working within areas covered by some of the CCGs or health boards to confirm accuracy of any commissioned service reported from a provider perspective. Data analysis was carried out by HJ (checked by JW) using Microsoft Excel statistical software (2016).

The survey content development was led by the British Liver Trust, the largest charity representing people living with liver disease in the UK, in collaboration with hepatology and primary care experts. As such, this survey was developed and operationalised with patient and public involvement throughout, with equality of input from professionals and public representatives.

Results

There were 159 responses to the survey, representing a 99% UK coverage of all UK CCGs and health boards. There was no response from two Scottish health boards. The survey covered three main

areas of engagement. The first addressed structural workforce and processes in place specific to liver disease; the second focused on the use of recommended guidelines and diagnostic tools to detect liver disease; and the third concerned engagement with more proactive risk factor-based detection of liver disease.

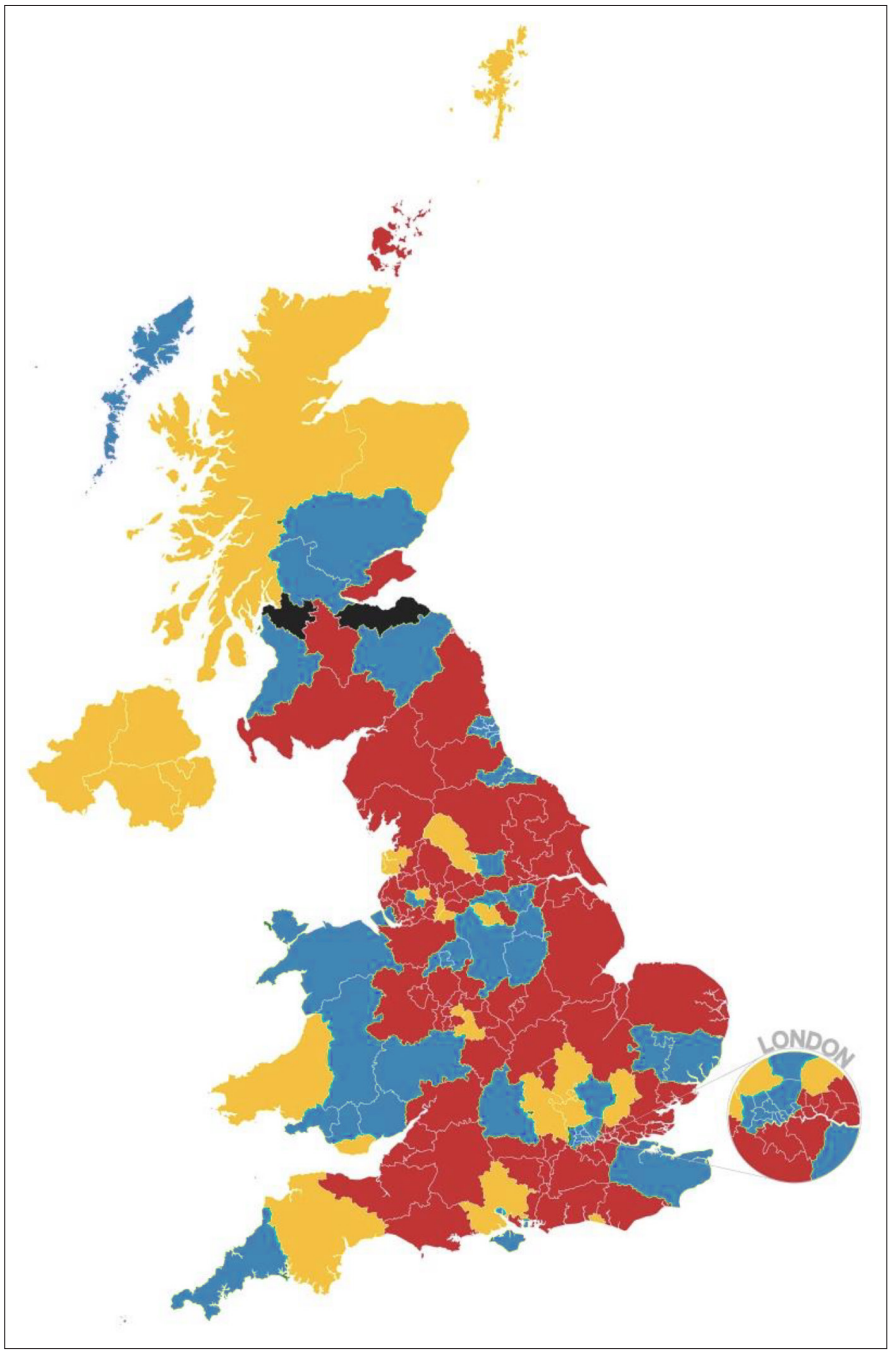

Figure 1 The availability of clinical commissioning group or health board-endorsed community liver pathways in the UK.

Key: red = no pathway for either the interpretation of liver blood tests or liver disease more generally; yellow = pathway for the interpretation of liver blood tests only or pathways in development; blue = pathways for both; black = no response to survey.

Table 1 UK clinical commissioning group or health authority structures in place relating to liver disease

	Named person responsible for liver disease *n* (%)	Pathway for assessing abnormal LFTs *n* (%)	Pathway for liver disease more generally *n* (%)	Processes in place to monitor adoption and efficacy of pathway *n* (%)	Monitoring of current local statistics relating to liver disease *n* (%)
England *n* = 135	20 (15%)	49 (36%)	36 (27%)	21 (16%)	45 (33%)
Northern Ireland *n* = 5	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Scotland *n* = 12	6 (50%)	8 (67%)	5 (42%)	0 (0%)	6 (50%)
Wales *n* = 7	6 (86%)	7 (100%)	5 (71%)	1 (14%)	4 (57%)
UK total *n* = 159	32 (20%)	64 (40%)	46 (29%)	22 (14%)	55 (35%)

LFTs = liver function tests. *n* = number of commissioning bodies.

Workforce and processes in place specific to liver disease

UK wide, only 20% of CCGs and health boards questioned reported having a named individual within their organisation responsible for liver disease. Only 40% had an endorsed pathway in place for acting on liver blood test results, with even fewer having pathways in place for other aspects of liver disease management. ***Figure 1*** provides a geographical overview of the provision of community liver pathways in the UK.

Very few survey responders (14%) were aware of any processes in place to monitor the adoption and efficacy of endorsed pathways. Just over one-third reported monitoring current statistics relating to liver disease locally. Further breakdown of these responses is shown in ***Table 1***. There was a marked variation across the nations in the UK, with Wales standing out as having prioritised workforce and processes focusing on liver disease within their health boards. Eighty-six per cent of health boards in Wales had a named liver lead in place, in stark comparison with the 20% UK average; an indication of the increased priority given to this disease area.

Table 2 The recommended management of liver disease in UK clinical commissioning groups and health authorities in relation to national standards and guidelines

Area of UK	Using BSG-endorsed LFT pathway *n* (%)	Using liver fibrosis assessment *n* (%)	Using indirect serum fibrosis markers[a] *n* (%)	Using direct serum fibrosis markers[b] *n* (%)	Using transient elastography[c] *n* (%)
England *n* = 135	50 (37%)	52 (39%)	56 (41%)	18 (13%)	26 (19%)
Northern Ireland *n* = 5	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Scotland *n* = 12	8 (67%)	8 (67%)	9 (75%)	6 (50%)	7 (58%)
Wales *n* = 7	6 (86%)	7 (100%)	5 (71%)	2 (29%)	7 (100%)
UK total *n* = 159	64 (40%)	67 (42%)	70 (44%)	26 (16%)	40 (25%)

[a]Included use of Fib4 score, non-alcoholic fatty liver diease (NAFLD) fibrosis score and AST:ALT (aspartate aminotransferase: alanine aminotransferase) ratio (other options given); [b]All but one response was for the enhanced liver fibrosis (ELF) test, single response hyaluronic acid.[c]All using FibroScan.

BSG = British Society of Gastroenterology. LFT = liver function test. *n* = number of commissioning bodies

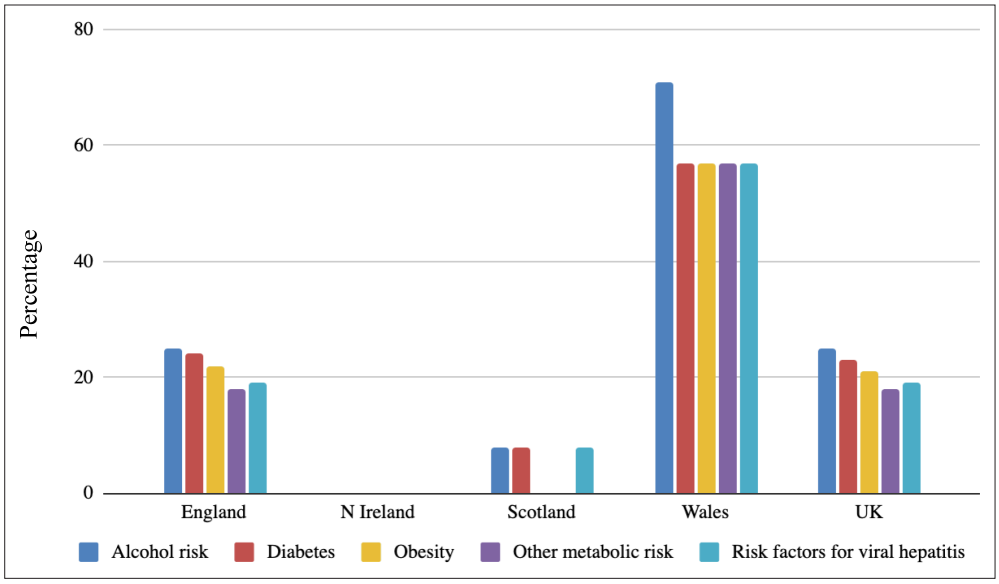

Figure 2 Percentage of clinical commissioning group or health authorities using proactive methods to identify liver disease by risk factor

The use of recommended guidelines and diagnostic tools to detect liver disease

Of those with pathways in place for liver disease, the vast majority were utilising pathways in line with current British Society of Gastroenterology (BSG) national guidelines with similar percentages of around 40% reported for both questions. Use of the indirect serum fibrosis markers, most commonly Fib-4 score and the NAFLD fibrosis score, were reported as being the most common CCG and health board-endorsed method of assessing for liver fibrosis. There was, however, marked regional variation with half (50%) of Scottish health boards utilising NICE-recommended direct serum markers (ELF test in the vast majority) in contrast with the 16% UK average, and 100% of Welsh health boards using transient elastography (FibroScan) as part of their endorsed pathways in contrast with one-quarter (25%) across the UK. The variable use of these diagnostic methods in detailed in ***Table 2***.

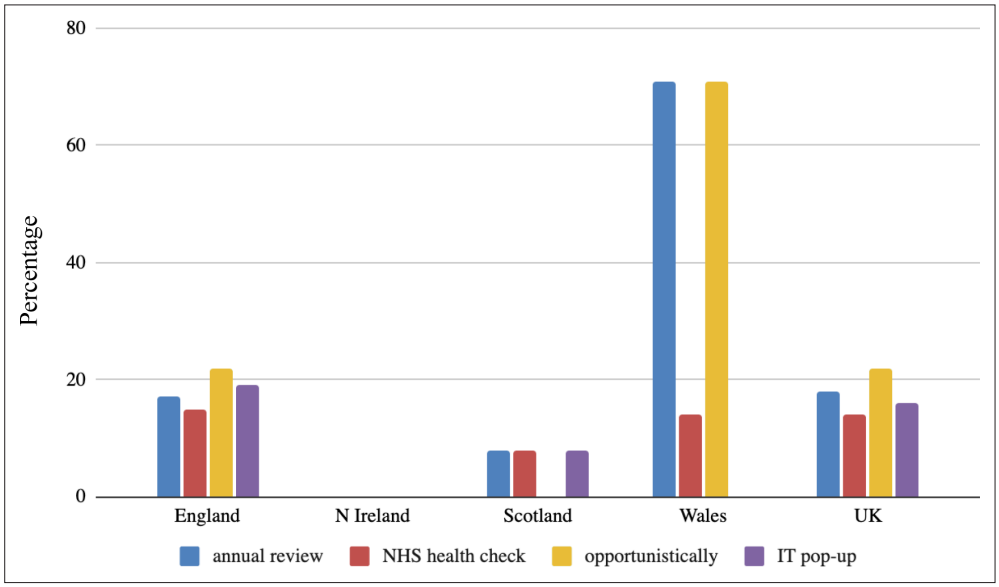

Figure 3 Percentage of clinical commissioning groups and health authorities using proactive methods to identify liver disease by assessment method

Engagement with more proactive risk factor-based detection of liver disease

Proactive assessment of those with known liver disease risk factors to detect disease was endorsed by around one-quarter (38/159, 24%) of CCGs and health boards. The most common risk factors taken forward for assessment were alcohol risk and diabetes. There was marked variation between regions in the use of these risk factors to detect liver disease with the most comprehensive risk factor-based strategies endorsed by the Welsh health boards (***Figure 2***). Of those who did proactively look for liver disease using a risk factor-based approach, common methods for identifying these patients were at already scheduled annual reviews (for other conditions such as diabetes, hypertension), NHS health checks, as well as opportunistically, and using developed IT-system pop-up (***Figure 3***).

The survey allowed for free-text comments to clarify and explain responses. Of note in the results presented is the lack of health board engagement in any of the response areas by those responding from Northern Ireland. Free-text responses clarified that Northern Ireland is in the process of working on a nationwide response to liver disease (liver disease is under the remit of a national specialist services commissioning team), including endorsing a computer-assisted decision-making tool for assessment of abnormal liver blood tests (based on a model developed in Tayside, Scotland[13]), as well as a NAFLD pathway, including fibrosis assessment, using indirect serum markers and FibroScan. This work has been delayed owing to the impact of COVID-19.

Discussion

Summary

This survey represents the only national comprehensive overview of commissioning for community management of liver disease to date.

It reveals variable commissioner and health board engagement with liver disease across the UK, in all of the areas surveyed. Overall, there were low levels of engagement across many areas from having a named liver disease lead, to commissioning services to allow for evidence-based management of people at risk of and with liver disease. There was marked regional variation, with Wales being the only nation with high levels of engagement in all areas surveyed.

Strengths and limitations

The limitations of a cross-sectional survey approach are well documented and this snapshot relied on the survey reaching a responder able to answer the survey questions accurately within the CCG or health board. The cross-checking with related providers, as well as the clear survey introduction in correspondence with all invitees, minimised this potential limitation. It is also acknowledged that individual GP practices may use their own templates and follow national guidelines to manage liver disease, independent of any CCG or health board recommendations. The survey results should thus be interpreted with caution when using them as a representation of individual clinician practice, although availability of diagnostics and the normalisation of pathways is likely to be driven at a regional level, meaning variation in individual practice is likely limited by these factors.

Comparison with existing literature

Although there is no directly comparable literature on commissioning of liver services in the UK, there are other data supporting the finding of stark and unacceptable regional variation in care for patients with liver disease. Public Health England (PHE) published the second *Atlas of Variation* in risk factors and health care for liver disease in England in 2017 and showed marked variation by CCG in levels of hospital admissions for liver disease (8.5 fold differences by CCG) and under 75-year mortality rates (7.7 fold differences).[14] The present study highlights a stark contrast in England between these clinical-burden measures and the managerial resource applied to liver disease. Although CCG boundaries have changed since the publication of the 2017 atlas, the lack of geographical matching between under 75-year mortality or hospital admissions for liver disease and the factors measured in the survey is clear, with high-mortality areas certainly being no more likely to have leadership or pathways in place (Supplementary Figure S1). Of the 15 English CCGs with the highest under 75-year mortality rates, 10 still have the same geographical boundaries. Only two have a named lead for liver disease,

only four have liver pathways, and none have a means of regularly reviewing their liver disease data. There have also been surveys looking at liver services from the provider perspective, again revealing marked regional variation in the provision of standardised pathways of care and access to specialist services.[15,16] Although this existing work differs from this survey in scope and outcomes studied, all this work supports the existence of a 'postcode lottery' in both health services available and outcomes for people with liver disease in the UK.

Implications for practice

The findings highlight the tangible difference that a regional policy initiative can make. The Welsh National Liver Plan ran from 2015–2020, a Welsh government response to the rising morbidity and mortality from liver disease.[17] One of the six delivery themes of the plan was that people with liver disease should be detected early and referred for treatment. Work within this theme included developing standardised referral pathways, with GP clinical champions working with health board liver disease teams to improve risk management, detection, and referral pathways. The stark difference between Wales and other nations of the UK within responses to this survey should act to incentivise policymakers to adopt and standardise evidence-based care for people with liver disease in their local populations.

CCGs in England are to be gradually phased out over the next year, with much of their remit being subsumed into new Integrated Care Systems (ICS) covering wider populations and geographies.[18] The findings of this survey, far from being redundant as a consequence of this, can provide valuable lessons moving forward. The ICS model is in many ways more aligned to the health board model in other UK nations, with the opportunity to reduce inequalities in care and outcomes for liver disease if a truly regional, integrated, evidence-based approach to detection and management is taken. A less fragmented system should provide opportunity for those commissioners with already well-developed community liver services in place to lead within new ICS areas, spreading effective practice rather than the need to develop new models. Royal College of General Practitioners-endorsed national liver commissioning guidelines provide a recommended defined standard of care to work towards.[19] Promoting these standards and considering incentivisation through QOF should be considered as further effective methods to drive change in the commissioning of community liver disease services, in response to these findings and other work.

This survey provides a UK-wide overview of system leadership of community liver services. The low levels of engagement and marked variation should be of interest to primary care practitioners, liver specialists, and policymakers. In an area of health care where there is a rising disease burden, the results of this survey should be used as a catalyst to drive change, reduce healthcare variation, and highlight necessary improvements to the primary care management of chronic liver disease in the UK.

Funding

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Ethical approval

As this study is a service evaluation survey that did not make use of any patient data, ethical approvals were not required or sought.

Provenance

Freely submitted; externally peer reviewed.

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3.3.1 PP4 commentary

In this comprehensive UK wide survey, with over 99% health board coverage, we analysed three areas of community engagement with liver disease care: Structural and workforce capacity, the use of recommended national guidelines and diagnostic tools, and engagement with a more pro-active risk factor based approach to the detection of liver disease in the community. The survey revealed stark inequalities across the UK in all areas studied.

Since the publication of this survey, and the discussion of comparative literature in the paper, data on both the national morbidity and mortality from liver disease (2) and on use of non-invasive liver tests in secondary care pathways (88) has been updated. National data continues to show stark inequalities in outcomes from liver disease across England (2). Although any causal relationship between these differences in mortality and availability of pathways of care in the community has not been established, the lack of comprehensive pathways of care in the community in the vast majority of geographical areas with the highest burden of liver disease morbidity and mortality can be seen as a health policy failure in getting care to those who need it the most. Two surveys exploring the use of non-invasive testing for liver disease in *secondary* care pathways, comparing data from a provider perspective from 2014/2015 with 2021 have shown significantly increased use and availability of these NITs over this six year period (88). It is hoped that this reflects increasing interest in making tests and pathways of care available, and this will reflect in improvements to community care for liver disease going forward. The formation of integrated care systems (ICS) in place of clinical commissioning groups (CCGs) in England represents an opportunity to use the data from our survey to highlight areas within an ICS footprint where comprehensive pathways of care are available, and discuss spreading this good practice throughout an ICS area. The British Liver Trust have been using our survey results to engage with ICS leads on this basis as a central part of their ‘make early detection of liver disease

routine' campaign (89). Our findings support the need for a national approach to reduce the postcode lottery of care for liver disease in the community.

3.4 Chapter summary

Pathways of care for liver disease in the community do exist in the UK, but they differ in their approaches between regions and are not available across the country. Newer tests to help find those most at risk of significant disease are becoming increasingly available in secondary care but are not available at the community level in the majority. Despite knowledge on risk factors for liver disease (highlighted in chapter 2) and improved diagnostic tests/research into a variety of care pathways (highlighted in this chapter) there is an implementation gap with limited national spread/uptake of these pathways of care. The work presented in this chapter highlights the need to explore the implementation barriers to more widespread uptake of pathways of care for liver disease in primary care. This is the focus of the next chapter.

Chapter 4: The experiences of primary care practitioners in managing liver disease: could this become routine primary care work

Evidence on who we should be identifying as at risk of liver disease, and what we are currently doing in the UK leads on to exploring why we are not currently managing liver disease in the community in a systematic, evidence based way for people at risk.

This chapter focuses on using qualitative research methods to explore the experiences of primary care practitioners in managing liver disease. The purpose of this section of work was to provide evidence to guide implementation of pathways of care for liver disease in the community setting. The papers within this chapter represent this iterative process with the first paper (Standing et al - PP5) providing valuable insight into GPs experiences of early detection of liver disease generally, followed by the paper by Jarvis et al (PP6) based on subsequent interviews with a wider range of primary care HCPs, and with a greater focus on the barriers and facilitators to liver disease care being implemented within the routine work of chronic disease management. The analysis of the interviews presented in the paper by Standing et al, in addition to the work carried out as part of the previous thesis chapters, guided the need for and content of the interviews analysed in the second paper presented in this chapter. The article detailed in Appendix A represents a further analysis of the interviews analysed in PP6 and is presented in full as written and awaiting journal review.

4.1 Qualitative methods and theoretical underpinning for presented papers.

4.1.1 methodological development towards the use of the normalisation process theory (NPT)

A qualitative approach was judged to be appropriate, for researching how liver disease management could become part of routine primary care work and understanding the reasons why this is not current practice. Quantitative analysis methods could not adequately research the ‘why not’ and ‘how to’ questions that needed to be explored, and where there had been little previous research in this field. My chosen focus was on the health care professionals involved in delivering and commissioning primary care. Semi-structured interviews were used to allow a variety of experiences and perceptions to be captured within limited time and resource. In my role as a primary care clinician researcher, I was observing practice and experiences alongside the interviews, and these insights have deepened my understanding of the wider context and challenges in this area of practice. Remaining reflexive and open around this with colleagues and the research team was an important part of the research process.

Early interviews were designed to broadly explore the experiences and perceptions of General Practitioners (GPs). Topic guides, data collection and analysis were approached at this stage without preconceived ideas and purposively not guided or limited by prescriptive frameworks of behavioural science and implementation. Data were analysed in an iterative way based on a constant comparison method rooted in modified grounded theory (90). Grounded theory was first developed by sociologists Glaser and Strauss (91). The concepts are not preconceived but ‘grounded’ in the data. The data collection, analysis and theory stand in close relationship with no preconceived theory but rather a preconceived area of study with the theory being developed from the data as it is analysed.

On the basis of these initial interviews, in addition to the work presented in chapters 2 and 3, it became clear that implementation challenges, and studying the implementation process in a formative analysis to guide liver disease pathway development, was a key next step. Understanding of the potential barriers and facilitators to developing a complex intervention of this nature (a liver disease detection pathway/framework) was felt to be best theorised and understood with the help of an implementation science theory. This focus on implementation is in line with good practice for complex

intervention delivery as outlined in the updated joint medical research council (MRC)/ national institute for health research (NIHR) framework for developing and analysing complex interventions (92). The iterative research process described so far in this thesis, had identified an implementation focus as missing from previous research. This focus to combine risk factor knowledge and availability of tests into effective (rather than just efficacious) pathways of care was identified as a research gap.

4.1.2 Normalisation process theory

In the second paper presented in this chapter (based on the later interviews with a wider group of primary care health care professionals), normalisation process theory (NPT) was used to inform topic guides for the interviews, as well as acting as the key theoretical underpinning for the analysis of the findings.

Use of a sociological theory for this phase of the research was felt to be important, to allow the progression from the development of robust explanations of what was being observed, to using these insights in the formation of practical recommendations. It made sense to use a theory that was developed in direct response to the observed difficulty of implementing new complex interventions in health service settings after recognising a gap in this theoretical space. NPT was developed after an extensive process; moving from the derivation of a set of empirical generalizations from the analysis of qualitative study data around health-care work and organisation, towards an applied normalisation process model (93), before road testing, analysing and extending to build a formal middle range theory of implementation (94). As a clinician reflecting on what I saw as a 'lack of action' rather than a 'lack of evidence' issue, I was drawn to the starting point of NPT: to understand implementation of an intervention demands looking at what the people involved actually *do* and how they *work* (95). As well as the core problem of implementation (the social organisation of bringing practices into action), NPT has a particular focus on embedding and integration. The theory postulates that practices become normalised as a result of collective and individual work which is enabled or not

through generative mechanisms: coherence, cognitive participation, collective action and reflexive monitoring (96). These generative mechanisms extended the earlier normalisation process model which was primarily focused on collective action to include explanation on sense making (coherence), means of involvement (cognitive participation) and the appraisal applied to the process (reflexive monitoring) (94,97).

Using NPT to guide qualitative interviews that were carried out to help develop and design an intervention (a liver disease detection pathway), i.e. as a formative rather than process analysis tool, is not 'usual' use of NPT. A systematic review in 2018 on the use of NPT in health care research showed its predominant role was in controlled and uncontrolled studies of process evaluations and feasibility studies (98). Only one of the 26 controlled studies included in the review used NPT in intervention design, and only seven of the 82 uncontrolled studies were classified as 'field studies' seeking to explore implementation using NPT around a broad research topic rather than the process of a specific intervention (98). The use of NPT in a formative evaluation, as employed in the interviews analysed in the second paper presented in this chapter (49) is felt to add to the implementation science literature on the usefulness of NPT in this context. If NPT, and other implementation science theories, continue to be used solely to explain why something that has already been implemented has either worked or not, opportunities will be missed. These theories could be used to improve the impact of interventions by shaping and improving implementation processes *before* implementation. This was my aim, in the presented papers below.

4.2 PP5 GPs' experiences and perceptions of early detection of liver disease: a qualitative study in primary care

Standing HC, Jarvis H, Orr J, Exley C, Hudson M, Kaner E, et al. Br J Gen Pract. 2018 Nov;68(676):e743–9. (48)

Holly C Standing, Helen Jarvis, James Orr, Catherine Exley, Mark Hudson, Eileen Kaner and Barbara Hanratty

GPs' experiences and perceptions of early detection of liver disease:

a qualitative study in primary care

Abstract

Background
The incidence of liver disease is increasing in the UK and primary care is a key setting where improvement in the detection and management of liver disease is required. Little is known about GPs' understanding and confidence in detecting liver disease.

Aim
To explore GPs' experiences of liver disease with a focus on early detection and interpretation of liver function tests (LFTs).

Design and setting
A qualitative study employing semi-structured interviews of a purposive sample of GPs from five UK primary care study sites.

Method
Telephone and face-to-face interviews of GPs were undertaken. Data were analysed thematically, using a constant comparative approach.

Results
From a total of 25 GP interviews ($N = 25$), four themes were identified from the data: test-requesting behaviour, confidence and challenges in diagnosing disease, access to specialist tests, and guidance and education. Participants' descriptions of how they request and interpret LFTs varied widely. Concern over missing diagnoses was a common reason for requesting blood tests; patients with mildly abnormal LFTs and those at risk of non-alcoholic fatty liver disease (NAFLD) were a particular cause of concern. GPs saw themselves as generalists, with a reluctance to take on specialist investigations. Guidelines promoted confidence for some clinicians, but others felt that liver disease was too complex to be amenable to simple instructions. Most felt that they did not have access to relevant, focused education on liver disease.

Conclusion
Liver disease is not perceived as a priority in primary care. If GPs are to take on a greater role in identification and management of liver disease, support is needed to promote awareness, knowledge, and confidence.

Keywords
early diagnosis; general practice; liver diseases; liver function tests; United Kingdom.

INTRODUCTION

The incidence of liver disease is increasing faster in the UK than in any other European country.[1,2] Liver disease is already one of the leading causes of premature mortality in the UK, responsible for 61 000 years of working life lost each year.[3] These rises are linked to increases in alcohol consumption and obesity.[4,5] The Chief Medical Officer and an all-party parliamentary group on liver disease have identified early detection as a public health priority, citing evidence that this will reduce disease progression.[6,7] Despite detection and management of chronic diseases being a major part of the work of general practice, there have been calls for urgent improvement in primary care for patients with chronic liver disease.[8]

Early detection of liver disease is a challenge. Many patients have few symptoms until the condition is advanced, when intervention may be ineffective. Liver function tests (LFTs) are a panel of blood tests commonly requested in primary care. However, LFTs on their own are poor diagnostic tools. Recent guidance from the National Institute for Health and Care Excellence (NICE) advises against relying on routine blood tests to rule out disease such as non-alcoholic fatty liver disease (NAFLD) and cirrhosis from all causes.[9,10] Interpretation of LFT results is not straightforward,[11,12] with algorithms developed to support GPs,[11,13] and only very recent publication of national guidelines to support the interpretation of abnormal liver blood tests.[14] A recent *Lancet* commission on liver disease has highlighted the need to improve expertise and facilities in primary care to strengthen detection.[3] Current evidence promotes the use of new investigations to detect the presence and severity of liver disease, such as serum tests for fibrosis and transient elastography.[15,16] However, these tests are not widely available, and GPs' understanding of their role in detection and management of liver disease in primary care is unknown. With multiple, competing priorities, it is not clear if GPs perceive early diagnosis of liver disease to be an important area for clinical education and service development.

This study explored GPs' experiences of identifying and managing all-cause liver disease, with a focus on early detection and the interpretation of LFTs.

METHOD

Design and participants

Qualitative semi-structured interviews were conducted with GPs from five geographical areas in England (North West London; Wessex; North East and North Cumbria; Yorkshire and Humber; Thames Valley and South Midlands). Participants were recruited via Clinical Research Networks and local networks of GP practices, using email invitations. Purposive sampling in the five areas ensured that a variety of

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How this fits in

Liver disease is a major cause of premature mortality in the UK; primary care has been identified as an area where major improvement is required. This study explored GPs' understanding and experiences of identifying liver disease. Findings from this study add to growing evidence of a lack of confidence among GPs in this area and identify non-alcoholic fatty liver disease as a particular area of diagnostic and management concern. Further research should focus on the most effective way of providing support, guidance, and training for GPs in the identification and management of liver disease.

perspectives and varying levels of clinical experience and knowledge in general practice, hepatology, or gastroenterology were captured (March to August 2016).

A semi-structured interview schedule was developed by the research team to cover topics identified from published literature, including GPs' experiences of requesting and interpreting LFTs and the availability of guidelines and educational resources on detection of liver disease. The interview guide evolved throughout data collection to enable exploration of emerging topics. When the data were judged to be sufficient and no longer developing in depth and complexity, recruitment ceased. Participants were interviewed face-to-face or on the telephone, and all interviews were audiorecorded and transcribed verbatim. The NVivo (version 10) software package was used to manage the data.

Table 1. Characteristics of study participants, *N* = 25

Variable	*n*
Sex	
Male	12
Female	13
Experience as GP, years	
<5	5
5–15	10
16–25	9
>25	1
Gastroenterology experience or training	
Yes	4
No	21
Size of practice, number of registered patients	
<5000	5
5000–10 000	9
10 001–15 000	9
>15 000	2
NHS region in England	
North West London	7
Wessex	8
North East and North Cumbria	5
Yorkshire and Humber	1
Thames Valley and South Midlands	4

Data analysis

The study design was informed by Glaser and Strauss's constant comparative approach.[17] Data collection and analysis ran concurrently throughout the study, analysis of early transcripts informed the interview schedule for later interviews, and early transcripts were revisited throughout the analysis process. Familiarisation with the data involved a detailed reading of the transcripts. This was followed by line-by-line and highlighting approaches for coding the data.[18] Field notes were used throughout analysis as part of the reflective process. To ensure the trustworthiness of the data, a proportion of the transcripts (20%) were coded independently by three researchers, before comparing and agreeing on themes. The wider research team, which included individuals with experience in general practice, hepatology, and alcohol and health behaviours, was involved in discussions around emerging themes.

RESULTS

A total of 25 GPs (12 male and 13 female) took part in interviews; two were conducted face-to-face, and 23 by telephone. Interviews lasted 15–50 minutes. Participants' clinical experience ranged from 3 years of GP training to >25 years in general practice. Only four participants had undertaken any specialist training in hepatology or gastroenterology. Practice populations served by the GPs varied widely in size and characteristics, from urban practices with a high degree of substance misuse to rural practices with primarily older populations. Characteristics of the study participants are shown in Table 1.

Four themes were identified from the data: test-requesting behaviour, confidence and challenges in diagnosing disease, access to specialist tests, and guidance and education. In the following section, quotations are presented to illustrate the majority and any extreme views.

Test-requesting behaviour

All of the interviewees reported that LFTs were part of routine practice in primary care. These were often ordered by other members of the primary care team as part of 'routine health checks' or to monitor

long-term medication use, as well as by GPs for symptomatic patients. Some GPs saw abnormal LFTs as a way to encourage patients to modify their behaviour, and used them in high-risk patients as part of a lifestyle intervention:

'You might do the LFTs just to sort of encourage people, because often, an abnormal result can make them feel that, actually, there is a problem and they need to do something about it.' (GP 16, partner [P], qualified >20 years)

Several interviewees admitted to using LFTs as part of a 'defensive medicine' strategy to avoid missing a serious diagnosis with an undefined problem. As a result, there was a feeling that too many LFTs were being requested, creating unnecessary work for GPs. This increase in workload had prompted some GPs to become more cautious, though they acknowledged that their decisions about when to request LFTs were not necessarily based on evidence:

'I try to have a reason to do it because I got the sense that you could find an abnormal test that's not significant. So, I deliberately think about why I need to do before I do them. So, I don't know of the evidence of when we should be doing them, so no, I don't do them in that way.' (GP 13, P, >20 years)

A number of the interviewees indicated that their decision to request LFTs was influenced by their perception of the potential benefits of treatment. If a possible diagnosis of liver disease would not affect the patient's outcome, they felt that testing for it was futile:

'I'm all for identifying people who have a condition that is going to have an impact on them, and trying to do something about that, but I don't know. Sometimes it feels, fatty liver for example is it …? What is the evidence that you can make any difference to that? If somebody is obese and has a fatty liver is there anything specifically an issue about their liver, or actually is it just part of the whole thing that it needs lifestyle change.' (GP 5, P, >20 years)

For some patients, participants suggested that efforts might be better focused on lifestyle intervention rather than testing for specific conditions.

Confidence and challenges in diagnosing disease

Although interviewees reported that they dealt with LFTs on a daily basis, this did not necessarily mean that they felt confident interpreting the results. Some of the GPs reflected that they were detecting fewer patients with liver disease than predicted by national statistics. This led to concerns that they were missing diagnoses:

'I slightly worry, having done this [interview] *that I'm missing some.'* (GP 15, P, >20 years)

However, others felt that they were competent at diagnosing liver disease and did not perceive it as an area where their practice needed improvement:

'I don't think it's an area where GPs are frequently missing the diagnosis or delaying the diagnosis. I think, because it's so easy to get LFTs, and because most diseases, whether its cancer, hepatitis, or alcoholic liver disease, they're pretty prevalent, you know, so we're used to dealing with them.' (GP 2, P, >20 years)

Diagnosis and follow-up of patients with NAFLD were identified as a challenge. Concerns related to identifying disease in high-risk groups, and knowing when to refer and how often to follow-up. Some of the interviewees felt that they may be overlooking diagnoses of NAFLD in high-risk groups. Currently, there is no universally approved method of identifying patients with NAFLD in UK general practice and several of the participants felt this may be contributing to missed diagnoses:

'I think we probably miss a lot of liver disease, which is non-alcoholic fatty liver disease, particularly in diabetics. We probably sit and wait on those patients more than we should be, and I think what we really should be doing is being a bit more proactive, and calculating a fibro score, and all the other things, so I think they're a group there where we could improve, as well.' (GP 1, GP registrar [R])

A diagnosis of NAFLD may lead to a referral to secondary care. Participants suggested that often the outcome of such a referral was lifestyle advice, which they felt could have been offered in primary care, saving specialists' time for more complex issues. A more confident approach to such referrals was proposed:

'We are sort of thinking, "God, what should we do? Let's let the liver specialists decide", even though they're just going, "It's a fatty liver, cut down his alcohol, control his

cholesterol." You think, "OK, I could've done that really. That's what we were going to do." So, I think giving us more confidence in managing the simple things, and then the consultants can actually get on and do the difficult things.' (GP 11, P, 13 years)

GPs in this study commented that they were unaware of any structured approaches for following up patients with 'mild' NAFLD. This led to concerns that evolving disease may be underestimated. It was proposed that, in line with other chronic diseases, there should be a recall system within primary care for patients with NAFLD so that this patient group would receive more standardised care:

'I guess, and this is what we're not doing at the moment that perhaps we should be with our fatty liver patients, you know, our patients who are diagnosed with fatty liver disease who aren't being — haven't needed referral up or being monitored by secondary care, whether we should have some in-house policy or way of monitoring them every so many years, just to see if there is any change in their blood testing. Rather than it just being a random thing, that it should be part of a sort of recall system. We haven't got that set up.' (GP 16, P, >20 years)

Minimally deranged LFTs, predominantly transaminases, are a very common finding in primary care. However, an abnormal transaminase result does not always reflect the level of the underlying liver damage. Participants commented that interpreting minor abnormalities in LFTs and deciding on a suitable course of action was a challenge, and could be a source of anxiety:

'It's quite easy to refer when you've got really abnormal LFTs and an abnormal ultrasound. It's the people that fall in the middle that are the most difficult so they're the people with the borderline raised LFTs, with maybe a little bit of fatty liver on an ultrasound but nothing else. They're the ones that are the most difficult. Do you just monitor? Do they still need referral? Are they at risk of future liver disease? I'd say they're the tricky ones actually.' (GP 23, salaried [S], 2 years)

Access to specialist tests

Alongside the standard LFT panel, most of the GPs in this study were able to make direct requests for ultrasound scans and extra diagnostic blood tests, which are usually referred to as the 'liver screen'. A majority of participants expressed a view that the role of the GP is as a generalist, and if extra investigations are required to make a diagnosis these should be requested by secondary care clinicians. Time pressures, alongside lack of specialist knowledge, were cited as reasons why further investigation was considered inappropriate in the primary care setting:

'I think we'll have to accept our limitations as GPs, and if there is anything more complex that's coming up, they're better off seeing the specialist than having me guess at what the results show, so I'm quite happy with what we have available.' (GP 7, P, 10 years)

The interviewees were prompted during the study to describe what 'any further tests' may entail. Some acknowledged that they were unaware of which additional tests may be available. A small number of the GPs interviewed suggested that additional investigations would be useful, in particular expanding the routine blood panel to include aspartate aminotransferase (AST) and direct access to elastography (fibroscan). However, it was recognised that any increased responsibility for requesting and interpreting results would need to be accompanied by education:

'As I said, we need, which are in the US, ultrasound elastography, we don't have direct access to that, to the ultrasound elastography, so that is something which might be useful. But it's having access, and also, another thing is educating us to interpret the results.' (GP 12, P, 16 years)

Guidance and education

There was no universal approach to the use of local or national guidelines to assist in the diagnosis of liver disease among the study participants. Some of the GPs were aware of local guidelines and used them regularly; others would search for help on national GP resource websites if needed. Several GPs were not aware of any specific local or national guidelines and a few admitted to knowing of guidelines, but choosing to employ their own systems devised from experience:

'I mean, the guidelines say, if you've got an ALT more than three times the upper limit of normal, repeated on one or two more occasions, then that would be a criteria; but it's not particularly one that I use, I would tend to monitor those.' (GP1, R)

When guidelines were used, they helped to increase GP confidence in their own diagnostic ability. These guidelines were

perceived to have had greater impact on clinicians' confidence where they were embedded in routine practice, with computer-based prompts or clear flowcharts:

'It just follows off the pathway, it's quite a clear flowchart, if this happens, does that happen, or if the other happened, refer on, based on what their fatty liver disease score would be. So, again, that would be using national guidance, when to refer. So, quite clear.' (GP 19, S, 2 years)

However, some interviewees suggested that interpretation of LFTs may not be as amenable to simple rules of interpretation, because of the variation in what an abnormal result may mean for the individual:

'I don't know whether it's possible to say, "If it's up above this amount you need to do this or below this ..." ... you know the way diabetes has flowcharts, "If the HbA1c is above this you do and if it does this you do this." You follow those quite clearly, whereas liver function doesn't really have an equivalent, like iron monitoring for warfarin. So, for other things we do follow quite strict guidance, but for liver function we don't really follow it so strictly. I suppose it's because it's so dependent for each person.' (GP 11, P, 13 years)

Most of the GPs interviewed expressed a desire for more education to help them effectively identify and manage liver disease. There was a consensus that liver disease was not currently promoted as a high-priority area for primary care. Some participants commented that tailored education around liver disease was limited:

'We [GPs] *pick and choose what we learn and therefore things that are easy, because they're throwing training at us, which they are for cardiology, for diabetes, and mental health, they're pouring that down our throats so we're jumping at all these things. But there's only a certain amount of days you have off to go on training and do things. Liver just hasn't been there at the front; therefore, I think people would've chosen it, but it hasn't really been available very much, so we've not done it. I think that probably is a problem.'* (GP 11, P, 13 years)

DISCUSSION

Summary

The present study suggests that liver disease is not perceived by GPs to be a particularly high priority, but it is an area where they lack confidence. Concerns were focused on missing diagnoses and uncertainty about how to respond to patients with mildly abnormal LFTs or those at risk of NAFLD. A reluctance to take on additional specialist investigations appeared to be rooted in GPs' perception of their role as medical generalists. Overall, liver disease was seen as complex and not a suitable topic for simple guidelines.

Strengths and limitations

This study describes GPs' perceptions of the diagnosis of liver disease, and the researchers believe it is novel in its scope. GPs were offered no financial incentives to participate, yet no difficulty was found in recruiting from any of the five geographical sites. Interviewees were self-selecting and were from practices known to local clinical research networks. However, the richness and breadth of the data imply that this was not a major limitation, with participants displaying a readiness to admit uncertainty or lack of confidence. The present study was conducted just before the publication of UK NICE guidelines on both NAFLD and cirrhosis.[9,10] These documents advocate a change to current practice. Participants may have been aware that guidelines were in development, but there was no time for them to have influenced experiences of diagnosing liver disease in primary care.

Comparison with existing literature

The researchers' findings of GPs' reported test-requesting behaviour are consistent with those reported in the qualitative arm of a large study looking at testing strategies for liver disease in primary care.[11] However, that study was focused on test-ordering behaviour, and, unlike the present one, did not explore GPs' experiences of diagnosing liver disease in any detail. The use of tests to change patients' behaviours, the defensive nature of testing, and the feeling that tests were requested too often were common themes in the present study. The findings reported here support the recent *Lancet* report, which suggests that primary care clinicians require clear guidance on the use of LFTs and the need for specialist referral.[3]

A recent study in North America explored primary care physicians' awareness of, and current practice related to, NAFLD.[19] Knowledge of diagnostic tools and understanding of the difference between 'fatty liver' and more progressive disease were found to be poor, though this brief online survey was unable to explore the reasons behind the findings. Several GPs in the present study indicated that NAFLD was an area they found challenging, in

particular, knowing how best to assess risks and follow-up patients. Clinicians suggested that referral often resulted only in lifestyle advice, which they felt could be offered in primary care. Other work beyond the UK has also identified NAFLD as an area where enhancing knowledge in primary care practice may be helpful.[20,21]

Difficulties over interpretation of minimally deranged liver function tests may be due in part to the well-documented discordance between blood test abnormalities and extent of liver damage. In other conditions managed by GPs, the relationship between abnormal blood tests, clinical decision-making, and pathology is often clearer cut, for example, in chronic kidney disease. GPs also reported varying use of guidance when managing liver disease. In contrast to other chronic conditions,[22] much local and national guidance on liver disease is focused on aetiological factors such as alcohol.[23] The relevance to patients with liver disease of different aetiology may not be apparent, even when the recommended management pathway is still appropriate.

Implications for research and practice

Findings from this study suggest that liver disease should be a target for improved practice in primary care and that GPs would be receptive to greater support and the promotion of a standardised approach to investigation and management. This will require adequate resourcing and a better understanding of precisely how to improve practice in this area. It is important to acknowledge that many determinants of the rise in chronic liver disease are social and political, and, for action by GPs to be effective, it will need to be part of a broader public health strategy. Work is underway,[6,7,14] but the development of up-to-date guidance, clinical tools, and educational initiatives is relatively recent.[9,10,14] Many GPs do not have access to recommended non-invasive tests, for example, transient elastography and blood biomarkers, and this will need to be addressed if the guidance is to be implemented.[9,10]

Early intervention can be effective for all the main causes of liver disease, including NAFLD,[24] alcoholic liver disease,[25,26] and viral hepatitis. The use of targeted brief interventions is supported by a growing body of evidence,[27,28] curative treatments have been developed for hepatitis C, and new antifibrotic medication will soon be widely available for all-cause liver fibrosis.[29] Crucially, all of these depend on awareness and early detection in primary care, and this is an area that urgently requires further research and development.

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Provenance

Freely submitted; externally peer reviewed.

Competing interests

The authors have declared no competing interests.

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4.2.1 PP5 commentary

This early exploratory interview study highlighted challenges faced by general practitioners in early detection of liver disease. Liver disease was felt to be complex and specialised with a perceived need for education to increase confidence. A majority of participants identified a lack of clear guidelines and pathways. They did not see liver disease as a high priority area. There was limited awareness and use of any of the more specialised tests to diagnose liver disease with some participants feeling they should be employed in the specialist setting. Although this paper is included in this later chapter due to the focus on the use of qualitative methods, this paper represents the first publication contributing to this thesis. Results from this work were used to guide the need for, and form of the subsequent qualitative work with a narrower focus on exploring liver disease management as routine primary care work in the context of chronic disease management. In view of the timing of publication of guidelines and standards on the management of liver disease by NICE (13,37,38) and the British Society of Gastroenterology (22), a general movement towards primary care being more aware of liver disease management in the UK had started to take place between these initial interviews and the subsequent interviews analysed in PP6. This allowed for more focused and richer narratives around embedding liver disease into long term condition management which would have been difficult in these earlier interviews.

4.3 PP6 Liver disease management as routine work in primary care: a qualitative interview study to guide implementation

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Helen Jarvis, Tom Sanders and Barbara Hanratty

Liver disease management as routine work in primary care:

a qualitative interview study to guide implementation

Abstract

Background
Morbidity from liver disease is rising in the UK. Most cases are caused by alcohol or non-alcoholic fatty liver disease (NAFLD) and treatable if caught early. Liver disease pathways have been shown to increase detection in the community, but have not been adopted into routine primary care work.

Aim
To explore primary care healthcare professional (HCP) experiences and understanding of chronic liver disease, and where it might fit into management of long-term conditions.

Design and setting
Qualitative interview study with 20 HCPs in primary care in the north of England.

Method
A semi-structured approach informed by a theory of implementation (normalisation process theory [NPT]). Data collection and analysis were concurrent. Interview data were analysed using thematic analysis.

Results
Participants identified the following key areas for action: incentivised frameworks and protocols to drive understanding, organise, and sustain practice; inclusion of common liver diseases into multimorbidity care to reduce complexity and workload; a need to define the GP role within a lifestyle-focused treatment pathway; and education/local champions to initiate and legitimise individual and organisational participation in change.

Conclusion
To embed chronic liver disease management in routine primary care work, researchers and policymakers must be aware of the implementation challenges. These findings can guide the adoption of effective pathways and help bridge the implementation gap.

Keywords
attitude of health personnel; disease management; implementation science; liver diseases; primary health care; qualitative research.

INTRODUCTION

Morbidity and mortality from chronic liver disease is rising in the UK. It is a leading cause of premature mortality with an average age of death in the UK from liver disease of 57.[1,2] Most cases of chronic liver disease are preventable and treatable if caught early and lifestyle interventions are enacted. Chronic damage to the liver is most commonly caused by excess alcohol, causing alcohol-related liver disease (ARLD), or obesity/metabolic risk factors leading to non-alcoholic fatty liver disease (NAFLD), or a combination of both. This increase in morbidity and mortality from liver disease contrasts sharply with decreases in the UK for other common long-term conditions.[3] Currently around 70% of patients who present to accident and emergency departments with decompensated (end-stage) liver cirrhosis have had no previous diagnosis or management for their liver disease.[3]

In UK primary care there are well established long-term condition management pathways for diabetes, cardiovascular disease, and many other conditions. These evidence-based approaches are often run by the primary care nursing team, with oversight from primary care physicians. This work has gradually evolved under successive NHS contracts and reorganisation, initially encouraged under National Service Frameworks (NSFs) and subsequently incentivised under the Quality and Outcomes Framework (QoF) scheme.[4] Introduced in 2004, the QoF is a system for the performance management and payment of GPs in the NHS.[4]

Chronic liver disease has been omitted from long-term condition management programmes in UK primary care and is not the subject of routine assessments or financial incentives. This is despite the fact that most annual reviews in primary care combine multiple long-term conditions within a single consultation, and liver disease shares risk factors with many other health problems. Primary care involvement in liver disease has generally been prompted by abnormal liver blood tests and focused on ruling out rare diseases and repeat testing. Guidance on appropriate response to risk factors and blood results, onward referral, or lifestyle interventions are inconsistent or absent. Several research studies have shown pathways to find chronic liver disease in the community lead to an increase in detection of significant disease[5,6] and are cost-effective.[7] Despite this, implementation of these pathways has been slow and partial[8] and there has been little prospective study of how they may fit within routine primary care work.

This study explored primary care healthcare professional (HCP) experiences and understanding of chronic liver disease, and how this might fit into long-term condition management structures. This is part of a programme of work that aims to use implementation theory to inform the development of a framework to embed the

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How this fits in

Chronic liver disease is common but not actively managed in primary care. It is unclear how liver disease pathways could fit into routine work in primary care. This study highlights some of the challenges to implementing liver pathways and key areas for action. Clinicians identified the need for a defined role in an integrated and legitimised pathway, which should be part of multimorbidity care.

management of chronic liver disease into routine primary care practice.

METHOD

Design

A qualitative cross-sectional study design used semi-structured interviews with HCPs working in primary care in the north of England (North East and North Cumbria). This study is reported in accordance with the standards for reporting qualitative research.[9]

Recruitment

Participants were recruited from across the north of England using local GP and primary care commissioning networks. Invitations to participate were cascaded out to practices by email. Sampling of responders was purposive to allow for a variety of perspectives from HCPs working in demographically different practices with varying levels of experience. Experiences of primary care nurses and healthcare assistants as well as GPs were sought.

Data collection

One author (a GP with expertise in liver disease in the community) conducted all the interviews via Zoom from October 2020 to May 2021. Interviews were digitally recorded, transcribed verbatim by a professional transcription company, and anonymised. Topic guides (Supplementary Document S1) were developed with reference to previous research with input from the wider project multidisciplinary group, including patient and public involvement (PPI) representatives. To provide an overall focus, while still allowing for flexibility, a semi-structured approach informed by a theory of implementation (normalisation process theory [NPT]) was used.

NPT is a middle-range implementation theory addressing factors needed for successful implementation and integration of interventions into routine work (normalisation).[10,11] It is divided into four constructs:

- Coherence: what is the work that people do to understand and make sense of a practice?
- Cognitive participation: what is the work that people do to engage and support a new practice?
- Collective action: what is the work that people do to enact a new practice, and make it workable and integrate it in context?
- Reflexive monitoring: what is the work that people do to reflect on and evaluate enacting a new practice in context?

As the aim of this study was to inform intervention development, the first two constructs were most relevant to topic guide development, although data collection remained flexible to the dynamic nature of these constructs and consideration of the wider context.[12]

The topic guide was modified in response to early interviews, as the data collection progressed. Data collection continued until it was judged that sufficient data had been collected with no new depth or complexity arising from the interviews.

Data analysis

Data collection and analysis were concurrent, with analysis starting as soon as the interviews were transcribed. Interview data were analysed using thematic analysis applying principles of constant comparison.[13] The NVivo (version 12) software package was used to manage the data for coding. Although NPT had been used to inform the topic guide and ensure data on the relevant issues were collected, an inductive approach to analysis was employed. This approach gave participants the flexibility to raise issues important to them, and did not constrain them to NPT categories. Each transcript was coded by the author who conducted the interviews. All transcripts were independently analysed by at least two authors, with regular discussions among paper authors to refine developing themes. A final set of themes was agreed on by all co-authors. In a second step of analysis the themes were interpreted using the first two constructs of NPT.

Patient and public involvement

This study sits inside a wider work programme of work, which has had significant PPI (both patients with chronic

liver disease and representatives from liver charities).

RESULTS

Twenty interviews were conducted online with HCPs working in primary care in the North East and North Cumbria region of England. Participants were GPs (n=13) and members of the nursing team (n=7), including nurse practitioners, practice nurses, and healthcare assistants. Interviews lasted 30–60 minutes. Demographic information is presented in Table 1. The list size distribution, profession, and experience level of staff and other documented demographics broadly fit with these distributions across UK general practice.[14]

Four themes that encapsulate the interviewees' views and perceptions are presented:

- structural barriers to operationalising liver disease care;
- liver disease as part of multimorbidity;
- the value in managing liver disease; and
- facilitators of change in liver disease care.

The quotes illustrate themes that came out of many interviews while also highlighting any outlying views.

Theme 1: Organisational barriers to care

Participants acknowledged that the two commonest causes of liver disease (ARLD and NAFLD) were 'chronic' in the sense that they required long-term management rather than acute treatment. Knowledge of the common preventable risk factors for liver disease was high. Despite this, the majority of participants shared the view that liver disease was not currently managed in the same standardised way as other long-term conditions within primary care. Reasons for this difference in approach to care for people at risk of liver disease were cited as primarily related to the organisational context and drivers of care, rather than individual clinical sense making.

To be considered a chronic disease in the primary care management context, it was felt that liver disease needed to be subject to protocols, with clear templates and guidelines. The primary care role was seen as being to implement and operationalise expertise brought together by others in clear guidelines, rather than to act independently to make clinical decisions outside of these protocols:

'The difficulty that I certainly find is that I never know – there's not a clear protocol. If you think like with diabetes you know what you have to achieve. You know what you've got to aim for your blood pressure, you know what your HbA1c should be, you know what urine sample should be, you know what the cholesterol should be, so there's very clear guidelines. With livers I think there's difficulty knowing when it's considered abnormal enough for investigation, what you then do with the results. When do you refer for a fibro scan, when is a fibro scan result important enough to need – it's a very woolly area which I think if it was clear guidelines that told you, "This is when you do x, y, and z." Again, I think it could fall into more of a streamlined chronic disease model.' (GP4, GP partner 18 years, cancer lead, list size = 9600 mixed/semi-urban)

The absence of QoF incentives for liver disease was highlighted. Participants pointed to the importance of systemic and IT changes that accompanied QoF, rather than financial incentives. These triggered processes for a comprehensive structured approach to management, and provided a prompt to remind them to take action in a given area:

'I think QoF is useful for concentrating the mind. I think it's never been a major driver in our practice. However, because the computer systems alerts and clever searches are often driven by QoF, I think things being on QoF benefit. So, for

Table 1. Participant demographic characteristics (N= 20)

Interviewee characteristics		*n*
Sex	Female	13
	Male	7
Role	GP	13
	Nursing team	7
Experience in current role	<5 years	6
	5–10 years	7
	>10 years	7
Interest in liver disease[a]	yes	2
	no	18
Size of practice, number of registered patients	<5000	4
	5000–10 000	10
	10 001–15 000	2
	>15 000	4
Practice setting	rural	6
	urban	10
	mixed/suburban	4
Practice demographics	deprived	8
	affluent	2
	mixed	10

[a]*Self-defined.*

example, in diabetes when recording microalbuminurea came off QoF the figures dropped from 80% to 60% and I don't think that's anyone deliberately saying, "Oh we're not getting paid for this now so we're not going to do it." It's about there weren't alerts on the computers and everything else.' (GP5, GP partner 35 years, diabetes lead, list size = 9500 deprived/urban)

Theme 2: Liver disease as part of multimorbidity

Some participants felt that liver disease was too complex to fit into a more structured clinical management approach. This perception arose in part from the custom of considering *all* liver disease as a diagnostic conundrum based on abnormal liver blood tests. When liver disease was framed in this context, participants were unable to see the relevance of other protocolised long-term condition care. As a result, active management of liver disease was more likely to be neglected:

'I think often a diagnosis as such of the liver disease is not made. So we get abnormal liver function tests for example and the response to that will quite often be simply to repeat the liver function tests after three months and then after six months and some people seem to get that continually and you look sort of two years down the line and they might not have had a liver screen done, so yeah I think it perhaps isn't as well managed as some of the other conditions both in terms of the diagnosis but – and the response is often to repeat the blood tests rather than to necessarily get the patient in and ask about alcohol, lifestyle, check a BMI [body mass index] *and those sorts of things.'* (GP11, salaried GP 7 years, list size = 4000 mixed/rural)

Where participants considered the common lifestyle-related chronic liver diseases (NAFLD and ARLD) as separate from the other rare liver diseases, it was easier for them to see the sense in a more integrated, structured proactive approach. NAFLD and ARLD shared common risk factors with long-term conditions already being managed in primary care. This was seen as key by the majority of participants.

On a practical level it made sense to participants for liver disease to sit alongside other chronic diseases and be considered as part of multiple long-term condition care. Emphasising the impact that lifestyle advice could have on the liver, as well as other conditions, was perceived as helpful:

'I think it's almost easier in a way because you say there's too much fat in your liver and I think people have a visual – can see that, can think what does that look like more easily than what does diabetes mean? Or what does high blood pressure mean? I think that's a really strong image for patients and they can see they're too fat and then there's fat in their liver …' (GP7, salaried GP 6 years, list size = 10000 mixed/semi-urban)

When participants considered embedding liver disease within existing structures for managing multimorbidity, they claimed that this would help to contain the workload. This was crucial when considering taking on new pathways of care:

'No, I think it would be quite easily encompassed in the screening because obviously we're doing bloods anyway so potentially we'll be looking at adding in a couple more bloods and obviously we'd be looking at patient's BMI and other sort of risk factors so I don't think potentially it would make a huge difference in the workload …' (Nurse [N]3, practice nurse 6 years, list size = 3500 mixed/rural)

Theme 3: Seeing value by professional role

The perceived value of identifying and managing liver disease seemed to relate to professional role. Nurses' positive approach to prevention and lifestyle interventions as treatment contrasted with the views expressed by some of the GPs. Doctors were more likely to link the value of liver disease management to the expectation of more 'medical' treatment. This tension led to some GPs struggling to identify their role within liver disease management and assuming, incorrectly, that other team members would not see beyond traditional doctor/patient expectations of a 'treatment':

'I guess the reason is because I don't perceive an active treatment or benefit from monitoring. You know, they come back, and their ALT [alanine transaminase] *is a bit worse next year. What am I going to do? Speak to them again and say, "You didn't really try hard enough with your diet? Are you still eating too much sugar?" or "I think you're lying to me about alcohol." I don't know. Awkward, awkward conversations'.* (GP2, GP partner, 21 years list size = 11500 mixed/urban)

In contrast, the nurse participants felt that a liver pathway in chronic disease

management would fit well into their current ways of working. They saw this as an extension of their established roles and expressed a willingness to be involved:

'I think if you can explain the fatty liver as a disease and what's causing it and why they need to change their lifestyle they're much more likely to engage with that. In a similar way to high blood pressure and diabetes, if you can really explain the relationships between these things and potentially they then see the results, so it's actually really satisfying for people if they can actually reduce their BMI and their liver function gets better for example or their HbA1c comes down, they can actually see that effort paying off …' (N3, practice nurse 6 years, list size = 3500 mixed/rural)

Theme 4: Facilitators of change in liver disease care

Education, legitimisation, and a local champion were seen as key facilitators to changing liver disease care in the community. Education gave practitioners confidence and allowed them to see the value of the intervention. This was noted as particularly important for the nurse participants to have effective and informed discussions with patients, despite not having been prioritised in any practice nursing curricula:

'We talk about alcohol and diet and things like that and it would be good to have some information to talk about liver disease for these certain patients so we can prevent things like that at first point instead of managing the condition later but no, we definitely don't really talk about anything like that to be honest. I've seen it on patients' notes but not been trained on it or anything. No.' (Healthcare assistant [HCA]1, healthcare assistant 6 years, list size = 5000 mixed/urban)

Prioritisation of a condition for inclusion in the QoF legitimised its importance and the need to change practice in that area. Participants gave this more weight than local pathways, as there was a perception that decisions made at national level had been through rigorous processes with more robust clinical reasoning from central decision makers. Such legitimisation was felt to be crucial to developing a common understanding among the whole practice team:

'Well, I think the whole point of it is its quality isn't it? It's not just the payment for it, it's also that it's seen at a national level that it's important enough to go onto QoF. I think also in terms of getting practice managers engaged in the process as well and having it more as a wider team. I think if you were going to put this down as a diagnosis you'd want to retrospectively perhaps look at your patients to make sure you had everybody who had fatty liver disease on the register. It's far easier to do that if you've got the practice management team on board and QoF definitely helps with that …' (GP11, salaried GP 7 years, list size = 4000 mixed/rural)

Participants stated that the importance they would attach to making liver disease a priority would also be enhanced by local colleagues within commissioning and secondary care. Someone championing change in an area of practice could make a lasting difference, and if this came from an 'expert' that was further evidence of the value of change:

'I think something like this which is probably quite a large-scale change in how we do things, I think probably we'd need somebody dedicated from the secondary care like gastroenterology setting who would actually perhaps work with some GPs who are particularly interested in the subject and develop a protocol between primary and secondary care that could be sent out to practices and adopted from there.' (GP4, GP partner 18 years, cancer lead, list size = 9600 mixed/semi-urban)

Interpreting the findings using NPT

Although the themes were not constrained by NPT, as this action-based theory of implementation was used to guide the study process, in a second analysis step the themes were interpreted with reference to NPT. Table 2 summarises the themes presented and how primarily the first two constructs of NPT, coherence, and cognitive participation, can be used to help interpret these themes and provide a focus towards the work that individuals and organisations would need to do to enable chronic liver disease management to become a normalised part of long-term condition care.

DISCUSSION

Summary

HCPs identified the lack of frameworks as a barrier to managing liver disease in a similar way to other chronic diseases. National frameworks such as QoF were seen to legitimise need and drive protocol

Table 2. Mapping themes onto constructs of NPT

Theme	Description of theme	Construct of NPT	Key area for action
Organisational barriers to care	HCPs describe views on liver disease being part of routine chronic disease management: • lack of framework/protocols • lack of QoF	**Coherence:** differentiation (difference from other routine practice) communal specification (shared understanding) **Cognitive participation:** enrolment (organising to collectively contribute) activation (actions to sustain practice)	Standardised protocols/ frameworks
Liver disease as part of multimorbidity	Understanding liver disease as part of long-term multicondition care: • complexity • separating NAFLD/ARLD • workload	**Coherence:** differentiation individual specification (individual sense making) **Cognitive participation:** activation	Work to incorporate common liver diseases into multimorbidity care
Seeing value by professional role	HCPs assign value related to how treatment is perceived and role: • seeing value in lifestyle interventions • role of GP (unclear) versus nursing team (clear)	**Coherence:** individual specification, internalisation (understanding the value)	Define a clear role for GPs in liver disease care
Facilitators of change in liver disease care	HCPs' views on what would initiate and maintain change: • education • legitimisation • local champions	**Coherence:** internalisation **Cognitive participation:** initiation (making things happen) legitimisation (right to be involved)	Promote education and local/ national champions

ARLD = alcohol-related liver disease. HCP = healthcare professional. NAFLD = non-alcoholic fatty liver disease. NPT = normalisation process theory. QoF = Quality and Outcomes Framework.

development. Considering liver diseases as part of multimorbidity was identified as a way of reducing complexity, and minimising the workload of adding liver disease to long-term condition care. The value of earlier detection was accepted by the nursing team but not by all GPs. Education and legitimisation were found to be important facilitators to the change necessary to make liver disease management routine in primary care. By analysing the results with reference to an action-based implementation theory (NPT) insight has been gained into the work that organisations and individuals may need to do to develop a framework for managing liver disease effectively in primary care. As this research is happening at the development stage of implementing an intervention, these findings fall mainly with the core constructs of coherence (sense-making work) and cognitive participation (relational work). To make sense of, and be able to build and sustain a new way of working in the area of liver disease, participants identified key areas for action: integrated and incentivised frameworks and protocols to drive communal understanding as well as organise and sustain practice; incorporating common liver diseases into multimorbidity care to reduce complexity and allow individual sense making as well as manage workload; defining the GP role within a predominantly lifestyle-focused treatment pathway for GPs to better understand the value in change; and education/local champions to help initiate and legitimise individual and organisational participation in change.

Strengths and limitations

To the authors' knowledge, this is one of the first qualitative interview studies to look at implementation of chronic liver disease management into primary care. Early detection of liver disease is high on the national and international hepatology agenda but this study is one of the first to give attention to the primary care perspective. The timing of this research is a strength, as it was conducted as part of the process of intervention development, rather than retrospectively identifying implementation barriers to a care pathway. Findings are therefore being taken forward directly to guide a local pathway implementation strategy. The validity of the study was strengthened by the use of an action-focused implementation theory (NPT). Participants were aware of the researcher's

professional background, which helped build rapport and a common understanding. However, it is acknowledged that this may have influenced the content of participants' narratives.[15,16] Limitations also include the possibility of selection bias, as participants who were willing to be interviewed may hold different views from those who were not. The interviews were conducted remotely rather than face to face as initially planned (owing to the coronavirus pandemic) and it is acknowledged that this may have influenced rapport and therefore data collected.

Comparison with existing literature

Several pathways to manage liver disease in the community have been developed and piloted.[5,6,17,18] Most are in the UK, and focused on short-term clinical outcomes such as the number of referrals to secondary care and new cases of liver disease detected. A retrospective study of 29 HCPs' experiences of specialist nurse-led clinics for community-based detection of liver disease identified some similar findings on barriers and facilitators to implementation. For example, practitioners required clear guidelines and responsibilities, and in this way saw themselves as functionaries of others' expertise.[19] In other work, the patient perspective on incorporating liver disease screening into community care has been studied.[20,21] Although the studies differed in patient groups eligible and tests offered, common themes around the utility of a positive test result to initiate lifestyle change by providing something concrete to work towards came across in both studies. These findings are closely aligned with the nurses in this study in seeing the value of making a diagnosis to prompt discussion and targets as part of lifestyle intervention.

Other studies have looked at the implementation of chronic disease management in primary care settings. A systematic review of factors influencing the implementation of chronic care models was dominated by work on diabetes pathways.[22] Of the synthesised findings related to HCP experiences, many of these were in common with this study, particularly within the theme of preparing HCP for change. Education for primary care practitioners, seeing a reason or value in change, and the need for supportive leadership to legitimise change were all recurring themes in the literature around management of other chronic disease. These themes, in common with this current study, support the findings and strengthen the recommendations for change, although none of the studies synthesised were related to chronic liver disease.

Implications for research and practice

The results of this study will be used directly to guide the development of a chronic liver disease framework being implemented into routine long-term condition management in North East England. Key recommendations for change are to standardise and integrate management protocols, incorporate liver disease into multimorbidity care, define a clear role for GPs, and promote education and local champions to drive these changes.

The study also adds to the literature on implementation science. The data-derived themes map well to the first two constructs of NPT, emphasising the validity and usefulness of this theory to guide and structure healthcare intervention implementation.

To make chronic liver disease management a routine part of primary care work, researchers and policymakers must be aware of the implementation challenges. These theory-driven findings can guide the adoption of effective pathways and help bridge the gap between research findings and real-world intervention success.

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Ethical approval

This study received approval from the Health Research Authority (HRA) (ref 20/HRA/3820). It also received ethical approval from Newcastle University (Ref: 3602/2020).

Provenance

Freely submitted; externally peer reviewed.

Competing interests

The authors have declared no competing interests.

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4.3.1 PP6 commentary

By narrowing the focus to chronic disease management in primary care, and how chronic liver disease might fit into these long-term condition management structures, this study was able to provide action recommendations for implementation. Structuring both the interview guides and the analysis with reference to the constructs of NPT increased the internal validity of the findings. It also allowed movement from inductive themes to a focus on the *work* needed to enable chronic liver disease management to be normalised in primary care. When using these findings to help design and implement a regional pilot pathway to detect liver disease (described in chapter 5), some of the key recommendations that were developed from the data were more easily seen to 'fit'. Reducing complexity and allowing individual sense-making by including liver disease in multimorbidity care, led directly to a study design for implementation that involved minimal alteration of existing annual review and health check templates. This meant including a liver health check alongside cardiovascular and metabolic conditions, rather than creating a whole new pathway of care for a 'new' condition. Likewise, the importance of education and local champions to help initiate and legitimise individual and organisational participation in change. This fed into a study design rooted in local GP champions working in collaboration with specialist colleagues; an approach that has already been recognised early into the pilot implementation as improving uptake.

In contrast, the theme that highlighted structural barriers to operationalising liver disease care prompted greater consideration of where primary care sits in the wider health system. The analysis presented in this paper highlighted the presence and importance of these more structural barriers, and touched on incentives. It did not explore in any depth the reasons why the barriers existed and who might have influence over them. Did the participants see themselves as having influence over these more systemic, structural barriers and if not, why not? Further analysis and development of this area was felt to be crucial in exploring implementation further and

is presented after further analysis of the interviews in Appendix A (article submitted and awaiting review).

4.4 Chapter summary

Primary care practitioners see liver disease as a complex and overlooked area, that does not sit within their chronic disease management work. Recommendations to change this, based on this qualitative research, with an implementation science underpinning, are to standardise and incentivise simplified pathways of care to sit as part of multimorbidity long-term-condition management. Collaborative working and education between primary and secondary care in developing and implementing change is key. There is, however, a recognition that the role of the individual GP in influencing this required work may be limited. Structural boundaries may lessen their ability to enact the change needed to incorporate this ‘new’ chronic condition into well developed and understood protocolised work.

Chapter 5: Evaluating the implementation of an embedded pathway for liver disease management in primary care

In chapter 3, I described how pathways to improve the detection of liver disease in the community have been developed and implemented in research and quality improvement projects (40,85,99) but seldom implemented into wider practice (47). The research presented in chapter 4 raised some of the implementation challenges and possible solutions based on work with primary care practitioners.

5.1 Co-designing a pathway to elucidate the optimal strategy of care

In addition to the implementation challenges considered above, there is also no consensus on test ordering protocols for cost-effective detection of liver fibrosis and cirrhosis in the community. There is some agreement that people with the highest likelihood of significant disease based on risk factors should be targeted, followed by a two-step approach using cheaper first line blood-based biomarkers with high negative predictive values, followed by more expensive, more specific tests. The evidence to support this has come from recent population studies in low prevalence settings (81). However, there is still debate around the utility of the simple tests in a general population setting, with some advocating that simple measures such as waist circumference may be as useful as biomarkers in deciding who may benefit from the more definitive investigations such as transient elastography (Fibroscan^{TM}) (100).

My secondary care colleagues in the north east region have been at the forefront of designing research to elucidate these optimum biomarker strategies and approached me to act as a primary care co-investigator on a study funded to define the optimal strategy across the primary/secondary care interface. This opportunity to collaborate and lead on researching the primary care implementation aspects of this study, using results from my doctoral work alongside extensive input from a regional liver patient support group (Liver North) has helped guide a novel study approach. The details of this

prospective observational cohort study to stratify liver disease in the community (SOLID) are presented in a protocol paper (50) led by Professor McPherson (Medical Research Council/NIHR Clinical Academic Research Partnership (CARP) funded reference: MR/V037331). The study protocol includes an outcome to assess barriers and facilitators to incorporating the pathway into routine primary care practice. There is a short summary of an analysis plan to assess this outcome which I led on within the protocol, in addition to contributing as a named author to the other sections. I will be leading on this process evaluation element of the study, which will be the next stage of my research.

5.2 Impact of formative evaluation on protocol development

The impact of my doctoral work on the development of this protocol, particularly the formative research into implementation challenges, may appear subtle. However, it has led to a radically different approach to previous research and quality improvement pathways for liver disease care. Previous pilot studies that have taken a research approach to finding liver disease in primary care have often used a primary care 'record search' to find at-risk patients, with a separate research team to collect data and manage referrals. This approach includes little engagement from the regular primary care clinical team (86). Other studies have developed commissioned pathways of liver disease care for primary care practitioners to follow, but have not integrated these into any routine ongoing care such as annual reviews or health checks. The additional workload often leads to low engagement (40,41). Restrictive inclusion criteria (e.g. MASLD only, abnormal LFTs only) have also led to confusion and poor use of pathways that do not relate to care of the person as a whole - core primary care work (40). Pathways that have been more integrated into routine care (e.g. liver assessments in routine diabetes checks (87), automation/reflex testing of routinely requested liver tests (101,102)) have been quality improvement/service innovation projects. They lacked the

ability to compare a variety of approaches and did not have individual patient consent for ongoing longitudinal follow up of clinical outcomes.

The approach taken in the SOLID study, is to maintain research rigour (fully informed consent of all participants, comparison of existing and novel biomarkers to elucidate best clinical pathway of care and permissions for individual long term follow up of clinical outcomes) with a pathway of care fully integrated into routine existing primary care structures. This allows for analysis of acceptability and implementation success to effectively guide wider roll out. Several key decisions in study design have meant this was possible. First, the consent process is carried out remotely by the research team before a planned clinical encounter is due to take place. This takes the additional work of consent away from the clinical team and allows for a near normal consultation where the 'liver health check' is incorporated into a long term condition or health check review. This incorporation of liver disease care into long term condition management was another key decision, guided by the importance of this being identified in the qualitative interviews with primary care practitioners, both to increase clinical sense making as well as minimise workload (49). This in turn has led to the regular primary care nursing team, particularly the health care assistants (HCAs) taking a leading role in running the study day to day, supported and legitimised by several GP study PIs working collaboratively with the secondary care CI. Recognising the key role that the primary care nursing team have in chronic disease work, and the value they assign to this work guided decisions around the importance of their key role. This has been supported by education, from involving them in site initiation visits (SIV) to regional teaching on liver disease. Allowing the research team to run remote consent, while training clinical staff to gather the study data and provide the clinical care has also allowed reach to both urban and rural practices not traditionally involved in research. Extending this to the training of local HCAs to carry out Fibroscans™ is also a novel approach to increase engagement, and in line with new NICE guidelines recommending the use of Fibroscan™ in the primary care setting (83).

Chapter 6: Discussion and conclusions

6.1 Principal findings

This programme of work used a step-wise approach to determine how best to deliver detection strategies for liver disease in primary care. Linking my principal findings to the initial objectives set out in chapter one:

Objective 1: Define who is at risk of common chronic liver disease in the unselected general population

This delivery must be based on targeting people in the general population at highest risk of significant clinical liver outcomes. The findings of my systematic reviews of population based cohorts (presented in chapter 2) contribute to our understanding of who these high risk populations are. People with type 2 diabetes, multiple metabolic risk factors and with co-existing alcohol consumption (now termed MetALD in the new nomenclature under the SLD umbrella (16)) should be considered as high risk MASLD groups, alongside the well-established risks of hazardous alcohol consumption and risks for viral hepatitis.

Objective 2: Review current pathways of care in the community for chronic liver disease in the UK

My research on care pathways for liver disease in the community (presented in chapter 3) has highlighted the postcode lottery of UK commissioning, as well as inconsistencies in the ability of current pathways to provide standardised, holistic care.

Objective 3: Research the experiences of primary care practitioners in managing liver disease and how this could become routine work

Challenges for primary care practitioners have been highlighted, in particular detecting and managing liver disease and implementing new pathways of care. Findings provide recommendations for successful implementation including the need to legitimise and incentivise pathways of care, and integrate liver disease management into established chronic disease care for people living with multiple comorbidities. Influencing change in chronic disease management requires buy-in from decision makers. My findings suggest that primary care clinicians feel limited in their ability to fulfill this role.

Objectives 4 and 5: Contribute to the design and implementation of a primary care pathway for detecting and managing liver disease

A regional primary care detection and management pathway for liver disease is currently being implemented and evaluated guided by the findings in this thesis. The pathway targets high risk individuals in the population and uses an approach based on integrating a liver health check within the management of other long term conditions. It involves the primary care nursing team as well as regional GP champions, with approval from, and an effective interface with secondary care.

6.2 Strengths and limitations of the studies overall

The body of work presented in this thesis used a mix of methods appropriate to the overall aim and individual objectives. This has allowed for an iterative approach to guiding improved liver disease detection and management in primary care. My work is unique in the fields of both liver disease and primary care research. The majority of translational and clinical liver disease research has been led from a secondary care

perspective and a focus on liver disease within academic primary care has been absent at both national and international levels.

The origins and design of this body of work are one of its major strengths. I initiated this research as a primary care clinician who had identified a clinical problem, designing a body of work to investigate and start to solve that problem for the direct benefit of patients and the public. The design of the research presented was guided and informed by a large number of key stakeholders. Crucially my work was co-developed with patient and public stakeholders as key guides. Representatives from LIVErNORTH (103) have been involved from the beginning, with a member / patient living with MASLD on the study advisory group, and regular PPI meetings held to enable input throughout the process. The British Liver Trust (104) is the biggest liver charity in the UK, and their director of communications and policy also sat on my study advisory group. The British Liver Trust acted as equal partners in the co-design of the national survey carried out as part of this thesis (47) and have been instrumental in disseminating the results of this work. The survey findings have developed into a central focus of their 'make early diagnosis of liver disease routine' campaign, involving work with Integrated Care Boards (ICBs) in England, Strategic Health Boards and members of parliament (MPs), aiming to reduce liver care inequalities in primary care across the UK (89). This is just one example of the strength of this multi stakeholder approach taken to my thesis that is already leading directly to healthcare impact.

There are some limitations to the body of work overall, as well as within the individual studies presented and reported in the published papers. For example, my systematic reviews were not limited to UK based studies, but the majority of included studies were published in English and retrieved data from mainly European and US cohorts (44,45). The results may not be applicable in cohorts from countries with different ethnic profiles. There are known differences in the body mass index (BMI) cut-offs that confer an increased risk of MASLD in Asian populations for example (105), as well as known genetic predispositions to poor outcomes in liver disease (106). This lack of heterogeneity may limit the utility of the findings for the development of pathways of

care for liver disease. This is a particular issue for the UK, where the socio-demographic and ethnic mix may differ from some of the US and European populations included in the reviews. In addition to these limitations, it is acknowledged that large population cohort studies are reliant on disease and mortality coding that varies within and across countries. A comparison of international estimates of MASLD prevalence with UK primary care data suggests that coding for MASLD is incomplete (4,36). There are also international differences in coding for risk factors. The true population at risk of having MASLD is acknowledged to be larger, and may be different, to the coded populations that formed the basis of the recommendations of the reviews.

Other study limitations relate to the measurement of the outcomes of preventive interventions. There is evidence for the benefits of brief alcohol (29) and lifestyle interventions in MASLD (30-32) but these tend to report short term outcomes such as reductions in alcohol consumption or weight loss and changes in liver enzymes/histology. Evidence is more limited for the benefits of earlier detection of liver disease leading to long term improvement in either patient reported quality of life or reductions in liver related morbidity and mortality. There is some limited evidence to show the benefits of these interventions in MASLD on all-cause mortality and cancer risk (107,108). There is also evidence that brief interventions based on known liver injury do impact on alcohol related mortality (109), and retrospective data reports lower liver mortality in MASLD amongst people following healthier diets (110). However, in developing pathways of care, several assumptions have been made around the environments needed to support successful lifestyle change (e.g. the availability of support for alcohol reduction and weight loss in the community) and the ability of surrogate end points to predict long term outcomes. Definitive data on the ability of early detection to reduce liver disease mortality can only be gathered with long term follow up of cohorts who have passed through these care pathways.

Research into liver disease associated with chronic hepatitis C has suggested that the diagnostic label may be responsible for a reduction in health related quality of life

(HR-QOL) (111). Other work has failed to confirm whether a reduction in HR-QOL with MASLD is due to the disease label or the condition itself (112). The work that I have presented did not directly consider the impact on patients of developing new pathways of care for liver disease. The potential for a new diagnosis of a chronic condition to cause patient anxiety/harm is an important consideration. This, as well as patient views on the potential of a liver diagnosis to empower and motivate, has not yet been explored. These are areas for future research.

6.3 Interpretation in relation to other studies

Each of the articles presented have discussion sections where I have interpreted the findings in relation to other studies. This has been complemented by the introductions and commentaries accompanying each of the relevant chapters. These arguments will not be repeated here.

It is interesting to compare liver disease with other conditions which have recently become part of routine work in primary care, and consider the process of implementation. Risk factors for chronic kidney disease (CKD) are well established, both for its development and progression (113,114) as is the bidirectional relationship between CKD and other cardiometabolic comorbidities (115). Twenty years ago in the UK, despite knowledge around these risk factors, CKD was poorly coded in primary care, blood results indicating significant CKD were not acted on according to guidelines and referral to secondary care was usually at end stage disease or not at all (116). This suggests a similarity with chronic liver disease, where knowledge of risk factors had not yet driven change in clinical care.

Several studies have researched interventions and pathways to improve the management of CKD in primary care. Key findings from this body of work have many similarities with the findings from my review of current pathways of care and exploring

the experiences of primary care clinicians in liver disease management. A comprehensive review of this literature in 2016 (117) summarised elements of successful interventions. Framing of CKD as part of the care for cardiovascular health and diabetes was key to understanding the importance of CKD. Interventions that were embedded and compatible with existing practices increased participation and reduced abandonment. Clinician involvement in feedback processes and improvements to the interventions increased sustainability (117). The literature in CKD also stresses the importance of proactive and collaborative research teams (118) and the advantages of clinical staff acting as local 'champions' to promote implementation (119,120). There are obvious similarities between common chronic liver diseases and CKD, with both sitting as part of cardiometabolic multimorbidity. Both are also important in contributing to multiple common outcomes, in addition to organ specific outcomes. This strongly suggests that the experience of implementing improved care for CKD supports the research findings in this thesis and may be useful to guide implementation of care pathways for liver disease.

Some of the differences between CKD and chronic liver disease may explain why liver disease has not been incorporated into chronic disease care in the same way as CKD. Some of these have been highlighted in PP5 and PP6, including perceived complexity in interpreting tests (48) and lack of legitimised incentives to drive change (49) (CKD has been included as part of the QoF in the UK since 2006). The other obvious difference is that CKD incorporates and simplifies the majority of common disease aetiologies into a single label. CKD does not differentiate in its nomenclature between aetiologies, but rather takes an approach based on progression of kidney damage, and has done for over 20 years (121)). Although nomenclature in liver disease was not fully explored in this thesis, this body of work, and other research has stressed the importance of simplification and unification of pathways and guidelines in liver disease (41,122). As discussed briefly in the introduction, the wider liver community has recently recognised the importance of nomenclature in helping to correctly frame, simplify and de-stigmatise chronic liver disease with consensus to change to an umbrella term of steatotic liver disease (SLD). This will encompass both alcohol related liver disease

(ALD) and the newly named metabolic dysfunction associated steatotic liver disease (MASLD) in place of NAFLD (16). Not only does this recognise the often overlapping aetiologies and similar histopathological process from steatosis to cirrhosis in ALD and MASLD, but the inclusion of the words 'metabolic dysfunction' should also help frame the condition solidly within cardiometabolic multimorbidity, one of the key recommendations to come from the findings of this thesis.

6.4 Clinical implications

6.4.1 Clinical recommendation 1: Incorporate common liver disease detection and management into the care of multiple long-term conditions

Findings from this research support recommendations from a majority of international guidelines to look for MASLD related liver disease in people with type 2 diabetes and those with multiple metabolic comorbidities (123-127). There is also a consensus on assessing for liver disease in people drinking alcohol at harmful levels (13,128). This thesis extends these guidelines by synthesising the evidence for this approach in unselected general populations and for those with dual pathology (MASLD with moderate alcohol consumption) (44,45). My work highlights that this is not currently being practiced across the UK (47) and provides recommendations on how this might best be achieved in primary care (49). One suggested approach is to embed this into chronic disease management reviews and routine health checks that are already happening, often on an annual basis in primary care. This is also in line with the developed SOLID study protocol (50). There is momentum in health systems research, driven by primary care clinicians, to consolidate disease reviews for people living with multiple long term conditions into one holistic annual review of care (129,130). This provides an ideal opportunity to consider liver health alongside cardiovascular and other metabolic health, allowing sense making of liver disease within this holistic care model. NHS health checks happen on a 5 year basis in people between the ages of 40 and 74,

specifically targeted at those without already diagnosed cardiovascular disease or diabetes (131). The guidelines for NHS health checks already advise screening for high alcohol consumption, and providing an assessment of liver cirrhosis for those drinking at potentially harmful levels (17). This is a recent addition, driven in part, by collaborative working during this thesis. The suggestion is, that in addition to incorporating a liver health check into annual chronic disease reviews, these five yearly health checks also act as an opportunity for a more general liver health check. This should incorporate the full implementation of guidelines on addressing alcohol harm, as well as looking for metabolic related liver disease in people with defined risk factors (i.e. new diabetics, multiple metabolic comorbidities identified during the check). This current gap in chronic disease detection and management in primary care (which already includes heart disease, stroke, kidney disease and diabetes) could be filled, as detailed in a proposed pathway detailed in Figure 2.

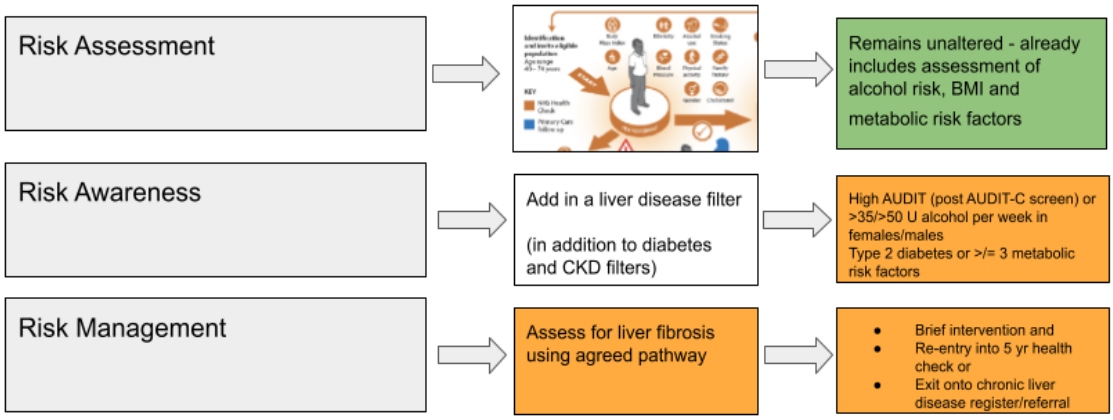

Figure 2: Proposal for incorporating common chronic liver disease (ALD/MASLD) into the 5 yearly NHS health check for adults aged 40-74 yrs.

6.4.2 Clinical recommendation 2: Educate health professionals around the place of liver health in their work

This work has revealed the importance of education with a broad range of health professionals. The qualitative interviews carried out as part of this thesis (49) highlight the key role that the primary care nursing team have in chronic disease care. I identified a perceived need for education and legitimation around liver health amongst primary care nurses, along with an established appreciation of the value of active intervention to promote liver health. A key clinical recommendation that arises from my work is that liver health should be addressed as part of primary care training for both GPs and crucially the wider primary care team. The move towards new nomenclature for fatty liver disease (16) may provide opportunity to accelerate this education, and allow for better sense making of liver health within metabolic dysfunction while cognizant of alcohol consumption. If, as expected, disease coding and clinical language used between primary and secondary care gradually change as a result of this new nomenclature, primary care needs to be equipped to confidently navigate this with other health care professionals and patients.

6.5 Implications for future research

My immediate next steps are a planned implementation process evaluation of the SOLID care pathway (50). I will have a particular focus on how well the pathway is being embedded into routine clinical practice, and the quality of patients' experiences, to guide further rollout.

Beyond this, the findings from my thesis have highlighted two broad areas for further research in the area of liver disease in the community:

6.5.1 Exploring the wider context of the introduction of new pathways of care

The qualitative work in this thesis has a focus on health care practitioners working at the coal-face of primary care. Although exploring challenges from the perspective of the working clinician is undoubtedly valuable, it has become clear during my thesis work and other linked collaborative work that the wider context in which these clinicians work is also influential. Primary care clinicians work within a wider health care structure where contracts, funding and direction come from an ever increasing number of health management bodies. NHS England, Integrated Care Systems (ICS) and Primary Care Networks (PCN) all exert influence on the day to day running of primary care, but the interplay of these healthcare decision-making structures with working clinicians in the early detection of liver disease is not yet clear.

In the qualitative work presented earlier in this thesis, I highlighted the importance of this healthcare context for interviewees (HCPs) to be *able* to participate in change (the introduction of a new pathway of care for liver disease). The early focus of normalisation process theory (NPT), which was used to guide the interviews and the analysis, was to characterise the generative mechanisms, or actions, that drive implementation processes. Later iterations of NPT (132,133) have, however, focused on the wider context in which these mechanisms operate, which are characterised as dynamic complex adaptive systems (132). Combining this extended NPT with linked realist evaluation strategies (133,134), and other frameworks with a greater focus on wider context (e.g. the Consolidated Framework for Implementation Research (CFIR)) (135) will be key to understanding the wider context of implementation.

Further research, underpinned by implementation science theory with a focus on the wider context, could explore decision-making in the management of liver disease throughout the healthcare decision-making structures.

An equally important area which has not been the main focus of the more exploratory research in this thesis, is the patient perspective and influence. There has been some

limited research on the acceptability of liver disease pathways in the primary care setting (136). However, these have not had a primary focus on how patients experience liver health as part of their long term condition management. Research has also not yet explored the potential benefits and potential harms of receiving a new liver disease diagnosis and where this balance lies from a patient/public perspective.

Further research is needed into the public/patient experiences of new ways of working in liver disease management. This will be started in the proposed work to evaluate the SOLID pathway, with planned interviews with patients to explore their experiences of participation. An understanding of their role, and the dynamics of the relationship between them and their healthcare providers, is likely to involve exploration of disease labeling, potential harms and benefits of diagnosis, as well as the role of pathways of care in tackling persisting well documented stigma around liver disease (104).

6.5.2 Reaching consensus on liver disease detection strategies - from testing to intervention to outcomes

My work (chapters 2,3) has identified a broad consensus on the need for earlier detection of liver disease in the community, focusing on people with defined risk factors. The most appropriate testing regime and outcome measures are still subject to debate. The SOLID study aims to define this optimum biomarker strategy (sequence of testing) across the primary care/secondary care interface and is currently in progress in North East England (50).

Choice of outcome measures in research into common chronic liver disease is problematic. To make early detection worthwhile, resulting interventions should aim to reduce morbidity and mortality from liver disease. However the slow disease progression means there is a paucity of long term data on the benefits of early detection and tailored intervention on liver related mortality. Pathways of early detection and management therefore use surrogate endpoints based on markers of fibrosis/cirrhosis

on blood tests, scans (the non-invasive tests) and in some cases liver biopsy. These surrogate endpoints, including the non-invasive tests have been shown to predict future clinical liver outcomes (137), and can be measured in proposed pathways of care. Further research is needed to standardise these outcomes and link them with the availability and uptake of lifestyle interventions. Ongoing prospective evaluation of dynamic changes in these surrogate outcomes after early detection of liver disease *with* intervention (weight loss or brief alcohol intervention for e.g.) versus detection without intervention will be a crucial step to further justify the benefits of early detection before the long term morbidity and mortality data is available.

The survey data presented in this thesis revealing a postcode lottery of commissioned pathways for patients at risk of liver disease in the UK would likely be mirrored if a survey of access to weight management services and alcohol reduction support across the UK were to be carried out. Commissioning of these services and therefore their availability in primary care is decided regionally with evidence that referral rates into weight loss services vary significantly (138) likely reflecting availability. Access to these services and the effect of this on realising any outcome benefits from earlier detection of liver disease is another key area for research. One way to approach this may be analysing the ‘natural experiment’ that is taking place with an already documented wide variation in access to primary care pathways, as well as intervention support, being analysed using large primary care datasets.

It is important to remember that the process of testing, communicating results and tailoring available interventions may not lead to any benefits for an individual patient. A diagnostic label may have an adverse impact on health related quality of life, and be considered as an ‘overdiagnosis’ if no effective treatment is available (139,140). This must be built into planning future research around early detection outcomes i.e. considering the potential harms and benefits as a balance to be holistically assessed using patient reported outcomes.

6.6 Conclusion

The overall aim of this programme of work was to determine how best to deliver detection strategies for liver disease in primary care. In conclusion, these detection strategies should focus on people at highest risk of clinically significant liver outcomes, be integrated into existing holistic, multimorbidity care pathways that are delivered with educational support and collaboration at all levels of care commissioning and provision.

Future research should focus on exploring implementation challenges, with a focus on the context of the healthcare environment from policy makers to patients. Further research is also needed to answer the important ‘so what now?’ question to ensure that finding liver disease early leads to improved outcomes for our patients in both the short and long term.

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Appendix A:

Jarvis H, Sanders T, Hanratty B. Liver disease as new work in the context of protocolised primary care - Do GPs have a role? A qualitative interview study.Chronic illness (under review)

Chronic Illness

Liver disease as new work in the context of protocolised primary care - Do GPs have a role? A qualitative interview study.

Journal:	*Chronic Illness*
Manuscript ID	CHI-23-0129
Manuscript Type:	Original Research Article
Keywords:	liver disease, primary care, implementation, qualitative, chronic disease

Abstract:

Objectives: Liver disease is common, but not part of routine chronic disease management in primary care. The aim of this study was to explore the challenges of implementing pathways of care for liver disease within existing highly protocolised structures in primary care.

Methods: Semi-structured interviews with 20 health professionals working in primary care. Interviews were informed by normalisation process theory (NPT) and boundary theory. Data were subject to thematic analysis.

Results: Three themes were identified relating to chronic disease work; definitions; need and worth, and roles. Participants identified that understanding and value of roles within chronic disease management were pre-defined by targets imposed on them as part of national incentives schemes. Structural boundaries constrained professional autonomy and the potential to influence this area of primary care management, including taking on new work.

Discussion: The inability to influence care decisions blurs occupational boundaries and goes to the core of what it means to be a professional. Unless liver disease sits within this target-based system, it is unlikely to become part of routine work in primary care.

Liver disease as new work in the context of protocolised primary care - Do GPs have a role? A qualitative interview study.

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Introduction

The organisation of General Practice has changed rapidly over the last 30 years. At the inception of the National Health Service (NHS) in 1948, general medical practitioners (GPs) retained a unique status amongst medical professionals as self-employed individuals. GPs were contracted and funded to provide services to the NHS, with payments primarily based on registered patient numbers. The imposition of the 1990 GP contract was the start of a gradual and persistent shift towards linking GP remuneration to meeting performance targets. Incentivised targets for providing health promotion/prevention and chronic disease management are now an integral part of modern general practice, with continued expansion at both national and local levels of government health policy. Performance targets in these areas have normalised the use of biomedical research evidence summarised in clinical guidelines and protocols, as a core component of good medical practice. This shift from high relative autonomy in practice towards implementation of evidence-based targets has been described by researchers as a fundamental shift in general practice towards a 'scientific bureaucratic medicine',[1] with imposed closer linkage to the wider 'health care state'.[2]

As a result of this orientation towards prevention and performance targets, many chronic diseases in UK primary care (particularly the ones incentivised by the Quality Outcomes Framework (QoF) introduced in the General Medical Services (GMS) 2004 contract)[3] are strictly managed in a routine, protocol driven way. This usually consists of an annual chronic disease check, with defined monitoring bloods and observations taken and then interventions enacted, aiming to move any disease parameters within the 'normal' or target ranges.

Liver disease, mainly due to alcohol related liver disease (ARLD) and/or non-alcohol related fatty liver disease (NAFLD) in the UK, is often chronic in the sense that it requires long term management and modification of known risk factors. Despite this, its management in primary care across the UK is variable with only a minority of areas reporting defined pathways of care for people with liver disease.[4] No liver disease outcomes have ever been part of the QoF or any other national incentivised schemes in primary care health policy. Its importance as a leading cause of premature morbidity and mortality has however been increasingly recognised, with earlier detection and management of liver disease cited in national commissions and guidelines as a key priority.[5,6]

The aim of this study was to explore with primary care professionals the challenges of care for a 'new' disease - chronic liver disease - being implemented in this protocol driven context. We aimed to study the role that targets, guidelines and incentives have played in chronic disease work, and to analyse how these structural boundaries have influenced the ability of primary care to take on new work and maintain professional roles.

Methods:

Design

Thematic analysis of qualitative data obtained through semi-structured interviews with health care professionals (HCP) working in primary care in the North East and North Cumbria (NENC) regions, England. The findings of this study are presented in accordance with the standards for reporting qualitative research.[7]

Recruitment

Participants were recruited from primary care commissioning networks in the NENC regions, with invitations distributed to eligible practices by email. Purposive sampling of respondents was used in order to capture a variety of perspectives intended to be broadly representative of differences in the demographics of populations served by participating practices and varying levels of experience among participating HCPs, with responses from healthcare assistants, qualified nurses and GPs all being sought.

Data collection

All interviews were conducted via Zoom between October 2020 and May 2021 by a single author (Author 1, a GP with a particular interest in the epidemiology and management of liver disease in primary care). All interviews were digitally recorded, anonymised and then transcribed verbatim by a professional third party service. A topic guide was developed (supplementary document 1); this was informed by previous research with further input from the multidisciplinary project group, including patient and public involvement (PPI) representatives. To maintain an overall focus while allowing for a degree of flexibility, we used a semi-structured approach informed by normalisation process theory (NPT).

By way of explanation, NPT is a middle-range implementation theory that addresses factors needed for successful implementation and integration of interventions into routine work (normalisation).[8,9] It is comprised of four constructs: coherence, cognitive participation, collective action, and reflexive monitoring, which can briefly be defined as follows:
coherence - the work that people do to understand and make sense of a practice;
cognitive participation - the work that people do to engage and support a new practice;
collective action - the work that people do to enact a new practice, to make it workable and to integrate it in context;
reflexive monitoring - the work that people do to reflect on and evaluate enacting a new practice in context.

As data collection progressed, the topic guide was iteratively modified in response to initial interviews. Interviewing continued until it was judged that no further depth or complexity was being added to the data.

Data analysis

Collection and analysis of the data were conducted concurrently, with analysis starting as soon as initial interviews had been transcribed. Interview data were coded using N-vivo software (version 12) and then analysed thematically by applying principles of constant comparison.[10] Although NPT had been used to inform the topic guide and to ensure that relevant data were collected, an inductive approach to analysis was employed whereby participants were not constrained solely to NPT categories, thus allowing participants the freedom to raise any issues that were of particular importance to them. All transcriptions were coded by the author who conducted the interviews before being independently analysed by at least two authors, with further discussion amongst authors as required in order to further refine any developing themes.

As analysis was ongoing, it became clear that professional boundaries, and the ability to control these boundaries, could help explain many of the implementation challenges that we were analysing in the data. Further analysis and retrospective re-coding of early interviews was therefore carried out, guided by boundary theory as a framework of explanation. Boundary theory explores how professional roles and boundaries between occupations have been

'constructed' at an individual and social level by practitioners to maintain occupational control and professional autonomy.[11] These micro level social processes where boundaries are constructed and negotiated are referred to as 'bounday work'.[12,13] Maintaining these occupational boundaries is felt to require securing a monopoly over exclusive areas of knowledge as well as tasks.[11] As well as these social/micro processes working dynamically to construct and maintain boundaries, there are often external system/policy/macro processes at play.[14] Individual professionals may have little individual control over these processes or 'system boundaries'.

A final set of themes was agreed on by all co-authors.

Ethical approval: This study received approval from the health research authority (HRA) (ref 20/HRA/3820). It also received ethical approval from Newcastle University (Ref: 3602/2020).

Results:

Twenty online interviews were carried out with health care professionals (HCP) working in general practice in the North East and North Cumbria region of England. Participants were members of the nursing team (seven) (including nurse practitioners, practice nurses and health care assistants) and GPs (13). Interviews lasted between 30 and 60 minutes.

Themes that encapsulate the interviewees' perceptions and views are reported. They all relate in different ways, to the role of structural boundaries in influencing understanding, worth and roles within chronic disease management. As interview topic guides were developed to examine potential barriers and facilitators to the effective implementation of a chronic liver disease management pathway in primary care, themes were also developed and analysed with regard to the constructs of normalisation process theory.

Direct quotations are presented to illustrate common themes whilst also highlighting any outlying views.

Definitions of chronic disease work

When asked about chronic disease management and how liver disease may or may not 'fit', participants employed an external or 'system' based understanding of chronic disease, rather than drawing on their medical knowledge. Participants defined and understood chronic disease as those conditions covered by guidelines and protocols, and on the 'usual' or 'standard' list. The lists were perceived to be external, fixed and handed down *to* them, rather than decided *by* them. Medical conditions that required long-term management rather than acute treatment, but did not sit on this defined list, were simply not discussed in the same way as a 'chronic disease.'

Well, it's defined by the disease they've got. Yeah so it's a limited number of diseases but not every disease clearly. We don't have an annual follow up for say osteoporosis but we do it for rheumatoid arthritis, we do for hypertension, diabetes, asthma. The usual stuff (GP13 - GP partner 30 yrs)

The majority of participants - both the GPs and the primary care nurses- saw chronic disease management being led and delivered by the nursing team within practices. The ability of the nursing team to lead in these areas seemed to enforce this 'set list' definition of what was understood by chronic disease. This understanding fitted with the primary care nursing team role being seen as very protocol and template driven.

I think there's that sort of standard list isn't there? That kind of hypertension, diabetes, as you said those are commonly seen as chronic disease. I would definitely say other diseases fall within the remits of GP-led disease rather than fitting into those clinics which are nurse-led. So probably a bit of nursing experience, what they are interested in and what they have experience in makes them confident to ***term*** *that a chronic disease. (GP12 -salaried GP 8 yrs)*

This externalised understanding of chronic disease work, as lists and standardised processes to be carried out by the nursing team, left little space for consideration of conditions that were not included. Participants acknowledged that liver disease and others may have an 'identity crisis'; being defined as neither an acute nor chronic condition. Several participants discussed their experiences of other 'new' conditions, particularly chronic kidney disease (CKD) making it into this chronic disease paradigm, citing the framing of CKD within cardiovascular and diabetes care as an important shift, in line with findings from a realist review on CKD management implementation in primary care.[15] This framing shift, along with the incentives, templates and protocols that followed, was widely accepted as having moved CKD from a condition perceived as having a similar identity crisis to liver disease ten years ago, into its current position as a managed chronic condition. Liver disease was not yet understood or defined in the same way.

The need and worth of chronic disease work

As well as defining an understanding of what chronic disease meant to participants, clinical guidelines, in particular the Quality outcomes Framework (QoF), appeared to override much of the individual practitioners' critical appraisal of any hierarchy of clinical need. Knowledge of liver disease prevalence and burden, and awareness of the common risk factors for liver disease were high amongst participants but this did not translate into clinical action to manage this group. The need, and by extension the worth, of work was externalised, leading to a feeling of powerlessness to intervene or change work priorities according to clinical need. This seemed to hold true even when there was internal disagreement between what the individual clinician saw as being good clinical care, and what was deemed to be needed according to the incentivised frameworks and guidelines.

*The network has their areas that you **have** to do and CCG push their areas that you **have** to do and actually you're almost spread too thin to try and do them all and you think , 'Oh gosh, something else that we've got to do on top of everything else and sometimes the things that are pushed are good, they're good for clinical care and other things aren't necessarily but you **have** to do them (GP8 - GP Partner 11 yrs)*

When participants were questioned on *why* chronic liver disease was not given the same attention as many other chronic diseases and managed in a structured way, the QoF was directly cited by many as the reason that templates and structured management developed. The absence of any QoF targets for liver disease was then a reason for deprioritising. Participants all distanced themselves from this decision making, again implying that they were powerless to influence 'decision makers higher up'. A minority of participants acknowledged directly the financial implications of the QoF system on influencing clinical priorities.

We've obviously got the QoF system which means that we've got boxes to tick in order to get money so that makes sure that chronic disease are manged because every practice wants to make sure that they get their income and therefore there's a motivational drive to do that. (GP3 - GP manager, previously GP Partner)

This neglect of non-incentivised aspects of care has been noted in other research examining the impact of financial incentives on internal motivation in UK primary care,[16] although the GPs in that study described this neglect as something 'others were doing' rather than directly relating this to their own practice.

When asked how management of chronic liver disease would change if certain aspects were incentivised, i.e. if liver disease 'made it' onto the QoF, there was universal acceptance that it would immediately transform into an area of need and worth. Participants described that their ability to carry out evidence-based reviews would be easier with the centrally commissioned templates, protocols and guidelines that would come with liver disease being added to the QoF. It was felt that the whole team would understand the value and need to carry out these reviews. This need did not relate to participants valuing liver disease as suddenly more clinically important, but rather the need to be guided by the QoF and what it contained.

*Well clearly **we have to** achieve various targets for QoF so that does guide us as to what we **need** to do at each annual review so if liver disease was part of that QoF process that would certainly up the ante because we would **have to** do it. I think it's a little bit of an afterthought at the moment so yes if that was incentivised that would definitely put it higher up the agenda (NP2 nurse practitioner -diabetes lead 14 yrs)*

A minority of participants shared their disquiet over the unintended consequences of financial incentives. Some disagreed with incentive driven care, arguing that the need and worth of work should relate only to improving long term health. When these participants criticized what they saw as the financial motivation of others, comparing it to their reported 'clinical-need' based

model, it was still based on being 'instructed' on what to focus on by others. Participants would need to be 'told' to improve work in a clinical area by others who were seen as the decision makers, rather than relying on their own medical knowledge. Even though the worth of the work to these participants came from a different motivation, the driver was still externalised.

Sadly, the more that I've done general practice I see people over the years who are colleagues at other practices who probably wouldn't see it as their job unless they were paid to do it. My feeling is that in primary care we look after people and actually if it's a way of improving health long-term then we should be doing it whether there's money attached to it or not. I think it is – to me it's core and there's various bits and pieces over the years that we have stopped ***having*** *to do therefore new things should replace it and if liver function or liver disease is the new thing to get on top of, yeah it should be something that if we are* ***told*** *to do we should just get on a do it. (GP4 -GP Partner 18yrs)*

Incentivisation of liver disease was seen as a crucial step by the majority of participants. Although other research in this area has found that internal motivation to manage established disease was not blocked by the introduction of the QoF, they also found the introduction of new conditions, not already part of routine practice, caused greater concern in diverting attention and challenging clinical autonomy, as with our findings.[16]

Defining roles in chronic disease work

Participants described defined roles within practices for chronic disease work. Health care assistants (HCA) and nursing teams were established as key practice staff carrying out the routine care. HCAs were perceived to be skilled at information gathering and following templates, whilst nursing staff monitor and interpret results according to clinical guidelines. Outcomes were often defined, with QoF providing target ranges for patient parameters, for example. Lack of complete autonomy in these nursing roles was generally accepted, and as long as there were clear instructions to follow, the nursing team were seen to be an easy 'fit' for liver disease management within these established roles.

From the healthcare assistants point of view they're already doing a lot and if you just include this in the lifestyle advice and the blood tests and things that they're doing and following the template I think that's absolutely fine, but I think the nursing staff are going to be more key if I'm honest in a lot of this rather than the GPs. It's not outside of their (nurses) scope of practice, it's not something that they're not competent to do. They absolutely are and they are the best people to deliver this, I would say. (GP3 - GP manager, previously GP Partner*)*

The role of the GP was less clear, more varied and had shifted over time due to the nursing team gradually taking on the management of those conditions well established on the chronic disease 'list'. This restratification of work within primary health care teams has been studied and interpreted as GPs accepting the need to follow guidelines but not allowing it to constrain the autonomy of *their* own clinical work.[17] The GP participants reported as a result of this, feeling

quite disconnected and powerless in chronic disease work. Some participants discussed a clinical lead role for GPs for specific chronic conditions, e.g. being the named 'diabetes clinical lead', but these roles were often felt to have been imposed at the time of the introduction of the QoF, and did not reflect GPs having developed and maintained a specific clinical interest in the area.

Do you think the reason that you have designated special interests in things is driven by targets and QoF?
Yeah , yep I do . I think I was lead GP for diabetes before QoF was invented a long time ago. Yah but I remember when QoF began we'd split up all the targets into between four or five of us. Yeah, worked out, who would be the lead for each one. That kind of stuck forever. (GP2 -GP Partner 21 yrs)

Although GPs were still seen as the 'leads' in many areas of chronic disease management they did not see themselves, and were not seen by nursing colleagues as having the ultimate decision-making role in setting the chronic disease management agenda. Participants had varying views of who fulfilled this role and who would need to be involved for chronic liver disease to become part of routine chronic disease work.

*I guess it's just not had the priority given to it **at a higher level** – from the point of view of putting it in to QoF and saying this is a chronic disease that needs to be managed in primary care from um, yeah from **decision makers higher up** I guess. It's not been prioritised in the same way. I don't know really. (GP3 - GP manager, previously GP Partner)*

A majority of participants claimed that although they were unsure of who exactly was filling this decision making role, they were sure these decisions on what was deemed worthy to manage as a chronic disease in primary care were evidence based. Others were slightly more cynical around the rigour of decision making.

It's a tricky one because there's such an emphasis on QoF that it can drown out smaller voices and it's whoever – I presume it's NICE who decide on the QoF indicators for each year, it's working out why some things are prioritised over others and the nature of the prioritisation and how – whether or not – it's almost like which group shouts loudest (HCA2 - health care assistant 3 yrs)

Participants suggested that the nursing team had a defined, protocol driven role in existing chronic disease management. The GP role was more varied and less clear, but GPs were perceived not to have complete clinical autonomy in this role which was left to higher level 'decision makers'.

Discussion

Summary and main findings

The areas that developed as themes within the analysis reflect the macro level drivers perceived to be setting the boundaries of work. The interviewees, despite the open nature of the questioning on chronic disease management in their clinical practice, rarely mentioned any individual factors influencing disease understanding, clinical prioritisation or role in chronic disease management, other than to comment that this individual prioritisation could only come after the core system driven elements were taken care of. These imposed system level boundaries reduced the ability of primary care professionals to set their own individual occupational boundaries and standards. Understanding, roles and responsibilities, and the value of this work were all channelled into an 'external system' paradigm.

The role of the primary care nursing team has shifted more easily to sit within this protocol/template driven way of working, perhaps due to the fact that any extension to their role into more autonomous decision makers has been fairly recent. Prior to the creation of nurse practitioners and nurse leads in disease areas in primary care, the nursing team saw their role partly as acting on behalf of other decision-making professionals (usually doctors) to fulfil set tasks. As a result, being part of the chronic disease management 'system', working to templates and protocols has seemed like a natural extension of this with perceived value and a defined role.

For GPs, on the other hand, the loss of autonomy imposed by incentivised standards has led to a 'dumbing down' within chronic disease management. In this situation, GPs are seeing themselves as functionaries of other decision-makers (health policymakers at various hierarchical levels). This regression in the ability to form individual and social 'micro' level occupational boundaries has led to a feeling of a lack of a role in chronic disease management, and an associated lack of responsibility, or worth, beyond the contractual obligations.

Strengths and limitations

The robustness of the study was strengthened by use of an action focused implementation theory (NPT) to help develop topic guide and interview structure and boundary theory to inform additional analysis. Participants were aware of the researcher's professional background which helped build rapport and a common understanding. However, it is acknowledged that this may have influenced the content of participants' narratives.[18,19] We can't be certain that participants views were representative of all primary care practice teams, but that was not the intention of the study. The interviews were conducted remotely rather than face to face as initially planned (due to the coronavirus pandemic). This may have influenced rapport and therefore data collected, but improved ease of participation and may have led to more frank discussion than in an more intimidating face to face research environment.

Comparison with existing literature

Several studies have explored the impact on primary care of a more structured management approach to chronic disease, particularly around the impact of QoF on practice organisation and care delivery. In common with our findings, extensive qualitative work in four GP practices in the UK found that QoF templates seemed to both define the nature of work required, but also act to discourage recording of information not deemed to be important to the 'process'.[20] Although general practice still promotes a definition of its core values being around patient centred, holistic practice, evidence in the field of chronic disease management related to QoF suggests a different reality. Evidence based medicine leading to centrally defined guidelines and protocols has led to researchers concluding that QoF 'pays doctors to conform' in the care of patients with certain defined health conditions, reinforcing a biomedical model of care.[21,17] Our study findings suggest that conforming in care is now so embedded that understanding, worth and roles in these chronic disease areas are 'set' with little room for care delivery in conditions that sit outside these structures. This lack of freedom to organise their own work expressed by our study participants has been felt by GPs since the introduction of the early performance targets as far back as the 1990 GP contract.[22] The gradual increase in the relative workload that meeting these targets requires, due to ongoing expansion of target types from an increasingly bureaucratic and multi-layered primary care health structure, (including primary care network (PCN) and integrated care board (ICB) level targets as well national QoF indicators) has only reduced autonomy in this part of clinical work further.

Defining roles and responsibilities in chronic disease management, and the impact on professional boundaries has also been widely researched.[23-25] Research analysing the 'tactics' general practices used to meet targets, reported the boundary work involved maintaining many of the traditional interprofessional hierarchies within this re-distribution process.[23] They found a move towards 'upskilling' at all levels with health care assistants taking on the nursing roles and nurses working more independently in chronic disease work, in line with our findings of well defined roles for the nursing team. What has been described as a role redistribution in chronic disease work, may be viewed through the lens of our findings as more of a substitution, with nowhere obvious to go for the GP within this. These studies had a predominant focus on the micro level social processes involved in boundary construction and assumed an internal focus of control in defining these boundaries, with the GPs involved often citing medical knowledge as 'setting them apart' from other occupations.[24,25] Our study found evidence to suggest that for the GPs, this assumed ability to negotiate their role in the context of expanding chronic disease care was being eroded, as the medical knowledge was now defined and handed down by external medical/managerial 'elites' (i.e the macro/system boundaries trumped the ability to negotiate the micro). Other studies have reported on this differentiation between groups of physicians into the 'rank and file' answering to the 'medical elites' and how this has affected GP clinical autonomy.[21,26]

Implications for future research/practice

This lack of clinical autonomy - defined as an inability of the individual physician to determine their own clinical practices and evaluate their own performances -[21] goes to the core of the definition of professionalism. Sociological literature has traditionally defined professions by traits/characterisitics that distinguish them from other occupations e.g. training, a body of knowledge and codes of ethics. This requires a professional to be able to construct and manage those individual and social boundaries between them and other occupations/team members - the 'boundary work' mentioned in the methods. The implications of not having control over this boundary work around chronic disease has implications for professional identity. This may just represent a *change* in identity to incorporate these different external parameters whilst still maintaining clinical autonomy in other areas of practice as suggested by previous work,[17] but exemplifies a worrying erosion of identity through external systems.

The findings should be used to help guide implementation of new pathways of chronic disease care (such as chronic liver disease) in the primary care setting. If, as suggested in this study, the understanding, perceived value and roles of chronic disease work are all determined by system level factors, rather than individual factors, then implementation needs to target those in positions of authority (those who still do have political decision making power within the medical profession). Alternatively the whole system needs to be adapted to allow time and support for conditions that don't make it onto the national agenda to be adopted as clinical priorities by individuals or practices - giving back that professional autonomy role to the coal face practitioners. With ever increasing numbers of targets in primary care, from every level of the health system structure, it seems the system will continue to hold the trump card. There is more need than ever for health policy makers to be held to account and their decision making scrutinised and questioned. If we fail to do this as a profession, then people with Cinderella conditions such as liver disease will continue to be forgotten.

Acknowlegements:

We would like to thank all the participants who agreed to be interviewed for this study.

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Protocol number:1.0. IRAS 278653

Topic Guide : Primary care liver disease framework - interviews with stakeholders

Note This is an inclusive topic guide, and questions will be omitted or modified, according to the interviewee's role in primary care liver disease management

- Details of current role and length of time in role

Understanding and perceived benefits of/problems with the management of chronic diseases in primary care:

What do you know about how chronic diseases (for example diabetes) are managed in primary care?

How does the management of chronic diseases differ from other work within primary care?

Has this changed over time since you have been in your current role?
Do you think there are benefits to this proactive management of chronic disease in primary care?

What do you think these benefits are?

Do you think there are problems with this current approach to chronic disease management?

What do you think these problems are?

Do you see any conflict between following protocols for chronic disease management and clinical autonomy/judgement?

Role within chronic disease management in primary care:

Can you tell me about your current role in chronic disease management, if any, in the primary care setting?

How managing chronic liver disease may fit or not into the chronic disease management structure:

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What do you know about chronic liver disease?

As far as you know, is liver disease managed as a 'chronic disease' in primary care?

If yes - which liver diseases are managed in this way?

If no - why do you think this is not the case?

Can you see liver disease fitting into the current structure of chronic disease management in primary care?

Do you see liver disease as different in any way to other chronic diseases?

If so, how?

Do you think managing liver disease more proactively like other conditions would be beneficial in primary care?

Do you see any potential problems with making liver disease part of chronic disease management in primary care?

Do you see any conflict between following protocols for chronic disease management and clinical autonomy/judgement?

Do you think this conflict would be any different in the management of chronic liver disease?

How a chronic liver disease management framework may work in primary care:

Thinking about the steps of:

1. **Finding those at risk of liver disease**
2. **Assesseing those at risk for liver disease severity**
3. **Offering lifestyle/other interventions for those with liver disease**
4. **Community follow up and referral**

(participants will have access to an outline provisional framework for managing liver disease in primary care)

Are you aware of the main risk factors for chronic liver disease (prompt if not) ?

How do you think it may work best to identify those in the community with these risk factors?

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In the primary care setting could this risk identification be integrated with other work ? (particularly thinking of other chronic disease management, routine health checks)

Do you think there is a role for more effective risk identification in the community outside of the GP practice?

What would you see as any difficulties in finding those at risk of liver disease?

Do you think GP systems (IT or other systems) could help in the identification of people at risk of liver disease?

Are you aware of any methods of assessing the severity of liver disease in those with risk factors or diagnosed disease?
(prompt re blood tests/fibroscan etc)

Do you see it as part of the role of primary care to assess this severity?

If novel methods of assessing for severity in the community were available (e.g fibroscan) what role would you see primary care having in requesting and delivering this?

Are interventions currently offered to those with liver disease?

What role do you think primary care has in offering these interventions?

Do you think currently available lifestyle interventions would be suitable for those with chronic liver disease?

Do you have a role in providing brief alcohol intervention in primary care and if so do you see this as valuable?

Do you feel there are good lifestyle services available for people with alcohol and non-alcohol related liver disease?

How do you think these could be improved?

Do you think patients with chronic liver disease should be followed up in the community and if so how?

Do you think this could fit into a chronic disease management/year of care structure as for other chronic diseases?

Would you see any problems with a more structured approach to follow up?

Developing a framework for managing liver disease in primary care: An interview study. Topic guide. Version 1.0

Date 20th July

Protocol number:1.0. IRAS 278653

How do you see the role of primary care overall in the diagnosis/management and follow up of patients with liver disease?

What would be your main concerns if a more structured approach to detecting and managing chronic liver disease was introduced in primary care?

(possible prompts re workload, autonomy, patient group being hard to reach, financial incentives etc)

How could these barriers be overcome if any identified?

Article commentary

The additional exploration and analysis presented in this paper highlights the important role that imposed structural boundaries play in influencing understanding of, roles and responsibilities within, and the value of chronic disease management work. GPs seeing themselves as functionaries, fulfilling their contractual obligations within the context of an imposed, fixed system suggests a need to focus more on wider context and influence when considering efforts to maximise implementation outcomes relating to complex interventions in primary care. This goes beyond description and recommendations around the *work* that is needed by primary care as individuals and an organisation for successful implementation, to thinking more about the wider context. Who has, or doesn't have, the *ability* within their professional influence to carry out this work?

Appendix B: Consent and ethical approval documentation

Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

NHS
Health Research Authority

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10 September 2020

Dear Dr Jarvis

HRA and Health and Care Research Wales (HCRW) Approval Letter

Study title:	**Exploring barriers and facilitators to developing a primary care management framework for liver disease**
IRAS project ID:	**278653**
Protocol number:	**NU-001209**
REC reference:	**20/HRA/3820**
Sponsor	**Newcastle University**

I am pleased to confirm that **HRA and Health and Care Research Wales (HCRW) Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further relating to this application.

Please now work with participating NHS organisations to confirm capacity and capability, in line with the instructions provided in the "Information to support study set up" section towards the end of this letter.

How should I work with participating NHS/HSC organisations in Northern Ireland and Scotland?
HRA and HCRW Approval does not apply to NHS/HSC organisations within Northern Ireland and Scotland.

If you indicated in your IRAS form that you do have participating organisations in either of these devolved administrations, the final document set and the study wide governance report (including this letter) have been sent to the coordinating centre of each participating nation. The relevant national coordinating function/s will contact you as appropriate.

Please see IRAS Help for information on working with NHS/HSC organisations in Northern Ireland and Scotland.

How should I work with participating non-NHS organisations?
HRA and HCRW Approval does not apply to non-NHS organisations. You should work with your non-NHS organisations to obtain local agreement in accordance with their procedures.

What are my notification responsibilities during the study?

The *"After HRA Approval – guidance for sponsors and investigators"* document on the HRA website gives detailed guidance on reporting expectations for studies with HRA and HCRW Approval, including:

- Registration of Research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics and is updated in the light of changes in reporting expectations or procedures.

Who should I contact for further information?
Please do not hesitate to contact me for assistance with this application. My contact details are below.

Your IRAS project ID is **278653**. Please quote this on all correspondence.

Yours sincerely,

Helen Poole

Approvals Specialist

Email: approvals@hra.nhs.uk

Copy to: *Dr Kay Howes*

List of Documents

The final document set assessed and approved by HRA and HCRW Approval is listed below.

Document	*Version*	*Date*
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [university insurance]	V1	01 July 2020
Interview schedules or topic guides for participants [Topic Guide]	V1	20 July 2020
IRAS Application Form [IRAS_Form_05082020]		05 August 2020
Letter from funder [Award letter]	V1	06 February 2020
Letter from sponsor [University sponsor letter]	V1	17 June 2020
Letters of invitation to participant [covering letter]	V1	15 July 2020
Other [Confirmation of PIC activity only]		05 August 2020
Participant consent form [consent form]	V1	15 July 2020
Participant information sheet (PIS)	3	07 September 2020
Referee's report or other scientific critique report	V1	17 June 2019
Research protocol or project proposal [NIHR proposal]	V1	22 June 2020
Research protocol or project proposal [research proposal]	V1	03 August 2020
Summary CV for student [Helen Jarvis CV]	V1	03 August 2020
Summary CV for supervisor (student research) [Supervisor CV]	V1	03 August 2020

IRAS project ID	278653

Information to support study set up

The below provides all parties with information to support the arranging and confirming of capacity and capability with participating NHS organisations in England and Wales. This is intended to be an accurate reflection of the study at the time of issue of this letter.

Types of participating NHS organisation	Expectations related to confirmation of capacity and capability	Agreement to be used	Funding arrangements	Oversight expectations	HR Good Practice Resource Pack expectations
There is only one site type in the study. The local CRN will undertake participant identification activity only.	PIC activities should not commence until a PIC Agreement is in place. HRA and HCRW recommend use of the standard Participating NHS Organisation to PIC agreement available here.	HRA and HCRW recommend use of the standard Participating NHS Organisation to PIC agreement, available here.	External funding has been secured from the NIHR Academy	No Principal Investigator or Local Collaborator are required at sites.	The sponsor has confirmed that local staff in participating organisations in England who have a contractual relationship with the organisation will undertake the expected activities. Therefore no honorary research contracts or letters of access are expected for this study.

Other information to aid study set-up and delivery

This details any other information that may be helpful to sponsors and participating NHS organisations in England and Wales in study set-up.
The applicant has indicated that they do not intend to apply for inclusion on the NIHR CRN Portfolio.

17th June 2020

Faculty of Medical Sciences
Newcastle University
Medical School
Framlington Place
Newcastle upon Tyne
NE2 4HH

Dear Dr Jarvis

Newcastle University Sponsorship of: Developing a primary care liver disease framework

Principle Investigator: Dr Helen Jarvis

Further to recent correspondence concerning the request for University sponsorship for the above named study, I am able to confirm that Newcastle University will act as sponsor for this project.

If there are any amendments to your protocol and research activity, please ensure that I am notified.

Yours sincerely

Kay Howes.

Kay Howes
FMS Research Manager

Study title: Developing a framework for the management of liver disease in primary care: an interview study

Interview consent form Thank you for reading the information leaflet about our research study. If you think you would like to help, please read and sign this form. Please initial the boxes below if you agree:

	Please initial
I have read the enclosed information sheet and have been able to download a copy to keep. I have been able to ask questions about the project and I understand why the research is being done.	
I understand that my participation is entirely voluntary and I am free to withdraw my consent at any time without giving a reason.	
I understand that interviews will be recorded electronically and transcribed (typed up). All recorded interviews will be destroyed after transcription, and my details will be removed.	
I understand that publications and reports produced by the study team may use direct quotations taken from interviews. The research team will ensure that I cannot be identified in these direct quotes.	
I understand that relevant sections of my data collected during the study, may be looked at by individuals from the research team, the sponsor or from regulatory authorities. I give permission for these individuals to have access to my anonymised data.	
I consent to my anonymised data being stored securely by the research team and used for future re-analysis	
I agree to be contacted by the study team after the study has been completed and would be interested in a future follow up study	
I agree to take part in the study.	

Name (staff member)	Signature	Date
Helen Jarvis		

Name (researcher)	Signature	Date

Appendix C: Invitation letters, participant information sheets and topic guides

Population Health Sciences Institute
Newcastle University
Campus for Ageing and Vitality
Newcastle upon Tyne
NE4 5PL
Tel: 07805 030385

Re: Invitation to take part in a research study about liver disease in primary care

We are conducting research into how best to manage liver disease in primary care, and identify acceptable, efficient ways of working. In this study, we plan to talk to a range of professionals who are involved in commissioning and delivering services. Your views and experiences would be an asset to our work, and we would like to invite you to take part in a short interview.

Please take your time to read the enclosed information sheet. If you may be interested in taking part, please contact us by telephone (07805 030385), email helen.jarvis2@newcastle.ac.uk or post (address above). We will be happy to answer any questions about the research. It yof are willing to take part, we will arrange a convenient time for an interview, either over the telephone or face to face.

This study has all the necessary approvals from a research ethics committee and the local NHS research governance body.

Yours sincerely

Helen Jarvis & Barbara Hanratty (on behalf of the study team)

Telephone: 07805 030385 **Email: helen.jarvis2@newcastle.ac.uk**

Study title: Developing a framework for managing liver disease in primary care: an interview study

Participant Information Sheet

You are invited to take part in this research study as an interviewee. To help you decide if you want to participate, it is first important that you understand why the research is being conducted and what it will involve for you. Please take the time to read through the following information carefully and discuss it with others if you wish. Please ask a member of the research team if there is anything you are unsure of, or if you would like more information about any aspect of the study.

This study is funded by the National Institute for Health Research (NIHR) and is part of a doctoral research fellowship. The study is sponsored by Newcastle University.

Thank you for taking the time to read this information sheet.

What is the purpose of this study?

The aim of this study is to investigate how best to manage chronic liver disease in general practice. We (researchers sponsored by Newcastle University) want to explore the views of professionals involved in looking after, or making decisions around the care of, people with liver disease. We are particularly interested in the possible barriers and facilitators to effective management of this patient group. Our plan is to interview staff in general practices, commissioning organisations and commissioned community providers.

What will happen if I take part?

If you decide to take part in this study, a member of the research team will arrange to interview you at a convenient time. If a face to face interview is not possible, particularly because of COVID-19, we can offer to interview you over the telephone or via microsoft teams/similar video technology. If a face to face interview is possible/preferred this will be arranged outside your workplace. The researcher will ask you questions about your experiences of current primary care for liver disease, how this compares to other long term conditions and explore how this could be improved. The interview will take 30-60 minutes, and will be recorded with your permission. These audio recordings will be transcribed (typed out) by a professional transcription service and stored securely and any information that could identify you, or your workplace, will be removed during this process. The audio recordings will then be immediately destroyed once the transcription has taken place.

What are the possible benefits of taking part?

We hope that by participating, you will be helping to improve general practice and community services for people living with liver disease. Following these interviews we hope to be able to develop new approaches to managing liver disease in primary care. Your participation will contribute directly to this work. You will receive £80 for participating to acknowledge the time you have contributed.

Do I have to take part?

Taking part in this study is completely voluntary. You do not have to take part if you do not wish to. When making your decision please consider the information in this document carefully and feel free to discuss it with others. If you do decide that you would like to participate, we will talk to you about what is involved, and answer any questions that you might have. Before starting the study you will be asked to sign a consent form using electronic written consent , confirming that you understand what is involved, and that you wish to take part. You will still be able to withdraw from the study after this point without having to give a reason. We will also seek permission to use your anonymous data in future research. This is optional and will not affect your participation in the study.

How will we use information about you?

In this research study we will use the information you give us during the interview. We will only use information that we need for the research study. People who do not need to know who you are will not be able to see your name or contact details. Your data will have a code number instead. Only the researcher carrying out the interview will know your name or contact details. One of the researchers collaborating on the analysis of the study works at Northumbria University. He will have no access to identifiable data.

Everyone involved in this study will keep your data safe and secure. We will also follow all privacy rules. At the end of the study we will save some of the data in case we need to check it and if you consent, for your data to be used in future research. All non-identifiable data will be stored for five years and then disposed of in a secure manner.

We will make sure no-one can work out who you are from the reports we write.If you would like a copy of the results sent to you personally, please get in touch with us using the contact details provided. In very rare circumstances, researchers find they need to tell someone else about what they have heard during an interview. This only happens if an interviewee says something which makes the researcher think that the individual, or someone else, is at risk of serious harm. In these situations, wherever possible, the interviewee is informed about any actions taken.

What are your choices about how your information is used?

During interviews, you do not have to answer any questions that you do not feel comfortable with. You can stop being part of the study at any time, without giving a reason, but we will keep information about you that we already have unless you instruct us otherwise. We need to manage your data in specific ways for the research to be reliable. This means that we won't be able to let you see or change the data we hold about you.

Where can you find out more about how your information is used?

You can find out more about how we use your information by asking one of the research team via the contact details listed at the end of this information sheet or by contacting the data protection officer at Newcastle University at wendy.craig@newcastle.ac.uk.

What if there is a problem?

If you have a concern about any aspect of this study, you should speak to a member of the study team who will do their best to answer your questions. Insurance for this study is provided by Newcastle University (underwritten by Zurich Municipal).

Contact details for questions and requesting further information:

Helen Jarvis
Doctoral research fellow
07805 030 385
helen.jarvis2@newcastle.ac.uk

Population Health Sciences Institute
2nd Floor BRB
Campus for Ageing and Vitality
Newcastle upon Tyne
NE4 5PL

Thank you for taking the time to read this information sheet.

Document S1

Topic Guide
Primary care liver disease framework: stakeholder interviews

Note This is an inclusive topic guide, and questions will be omitted or modified, according to the interviewee's role in primary care liver disease management

Aims and objectives

The main objective of this study is to explore experiences of managing chronic disease in the community and the barriers/facilitators to liver disease fitting into this structure. The findings will be used to inform the development of an implementable framework for the management of liver disease in primary care.

Main objectives/themes to explore:

- Current roles within and experiences of managing chronic disease in the community
- Awareness and experiences of chronic liver disease management and how/if this fits with current chronic disease management structures
- The steps necessary to manage chronic liver disease proactively in the community
- Barriers and facilitators to managing liver disease as a chronic disease within a framework/structure
- Covid-19 effect

1. Introduction

Aim: To introduce the research and set the context for the discussion

- Introduce self and Newcastle University
- Introduce the study: who is it for and what it is about
- Talk through key points:
  - Purpose and length of interview
  - Voluntary nature – right to withdraw, confirm consent
  - Recording
  - Conversation – not survey, test – no right/wrong answer
  - Thank you voucher – consent to email it
  - Confidentiality, how will be reported
  - Any questions before start recording

2. **Basic demographic and role information:**

Current role
Age
Gender
Length of time in job
Rural/Urban practice
Practice size
Any specialist interest/role in liver disease
How would you describe your practice population: (features, problems, socioeconomics, drug/alcohol use)

3. **Current roles within and experiences of managing chronic disease in the community**

Aim: To understand the perceived benefits of/problems with the management of chronic diseases in primary care

- Current role in chronic disease management, in primary care/community
- How and who manages chronic diseases (for example diabetes) are managed in your practice/in primary care
- Views on YoC/annual review approach - ? prescriptive v helpful?
- Attitudes to use of templates - centralised (e.g ARDENS v local)
- How /if the management of chronic diseases differ from other work within primary care
- Attitudes towards chronic disease management – who responsible, level of interest
- Changes over time in chronic disease management since been in role
- Benefits to this proactive management of chronic disease in primary care
- Problems/challenges with this current approach to chronic disease management*

*Possible prompts – clinical protocols v exercising clinical judgment/autonomy, areas of conflict, time pressures

4. **Awareness and experiences of chronic liver disease management**

Aim: To understand current experiences of managing chronic liver disease and how this may/may not fit with other chronic disease management structures

- Awareness/knowledge of chronic liver disease – prompt re alcohol and NAFLD
- Size of the problem in your practice

- Views on current management of liver disease
- Managed as chronic disease?
- Which liver diseases thinking of
- Why say is/isn't managed like other chronic disease
- How do you think it should be managed - primary care, specialist, who in practice?

- If not managed as chronic disease:

- Would it fit into current structures/could it be – expand why/why not?
- Is/how is liver disease different from other chronic diseases?
- Views on potential benefits re managing as a chronic disease?
- Views on potential problems
- Guidance/support needed to manage liver disease better in primary care?

- If already managed as a chronic disease:

- How/does this work?
- Is/how is liver disease any different from other chronic diseases?
- Benefits/problems experienced?

- Thoughts on clinical autonomy/judgement – liver disease – any other considerations on this v other chronic disease?
- Do you see as an isolated/separate condition or part of multimorbidity.
- How do sociodemographics of those with liver disease affect care
- Why not currently managed as for other chronic disease? why not a priority?
- How do you feel about this?
- Do you think those with liver disease different/stugmatised/unhelpable/unlikeable?

5. **<u>Conceptualising a chronic liver disease management framework in primary care</u>**
   Aim: To explore experiences and thoughts around how a chronic disease management framework for liver disease might work in primary care exploring steps

- Explore thoughts on identifying high risk individuals for liver disease (metabolic risk/alcohol)
  - How

- Where may fit in other routine work*
- Potential problems
- Ideas to make easier
- Where?
- Do you currently have a concept of 'risk' for liver disease and where does this feature?

*potential prompts around similar RF as for other chronic disease, routine checks, use of IT opportunistically in consults etc , outside GP – other community environments?

- Explore experiences and thoughts around effective triage for most at risk of severe disease
  - Awareness and experience of methods
  - See as part of role – why/Why not
  - If more tests available – what role would see primary care having.
  - Suggestions on use

- Explore experiences of lifestyle interventions for liver diseases
  - Awareness of availability
  - Role of primary care in offering /who else
  - Non disease tailored lifestyle interventions – suitability for liver disease
  - Views on how effective/barriers to these interventions
  - Do you see as role od GP/primary care to drive behaviour change?
  - Suggestions to improve

- Explore experiences of community follow up and referral for people with chronic liver disease
  - Should/how should be followed up
  - Primary care role
  - How might fit into current recall structures
  - Barriers?

- Overall thoughts on role of primary care in overall diagnosis/management/follow up of liver disease
  - Main barriers/facilitators to this happening
  - Resourcing – how do you think should be funded supported?

- Actionability of a framework ** key questions*

  - Does it make sense to you to have a new framework for liver disaese?
  - How likely is it that you would use it and how?
  - What would make you use a new framework?
  - Who do you think would be key in the team to getting this up and running?
  - (top down and practice level)
  -
  - How would you feel about a new way/framework to manage liver disease?
  - What should be the aim of the framework – support, protocol, algorithm
  - How would this fit into a practice routine?

6. **<u>The Covid-19 effect</u>**

Aim: To explore how the participants experiences of managing chronic diseases has been changed/influenced by Covid-19 and how this may impact on future disease management frameworks

- Role in managing chronic disease during the pandemic
- Any lessons that may be taken forward/continued
- Extra challenges raised
- Influence on responses in this discussion
- Anything pertaining to liver disease in particular
- Influence on the prioritising of health care – is this topic less/more/similar importance than previously

Summarising:

- **Any other issues/questions about the research they would like to raise**
- **Thanks for time**
- **Reassure about confidentiality**
- **Advise will email voucher of thanks**
- **Ask if would like to be informed of the outcomes of research and if happy to be contacted by email in case of need to clarify/invite for re-interview later in research**

Appendix D: Co-authorship forms

SUBMISSION BY STAFF CANDIDATES FOR THE DEGREE OF PHD BY PUBLISHED WORK

CO-AUTHORSHIP FORM

This form must accompany any submission of a joint authored publication for the degree of Doctor of Philosophy on the basis of published work.

A candidate should submit a separate form for each jointly authored work which is submitted for the degree.

TITLE OF PUBLICATION (article, book, chapter, monograph)

Metabolic risk factors and incident advanced liver disease in non-alcoholic fatty liver disease (NAFLD): A systematic review and meta-analysis of population-based observational studies__

DATE OF PUBLICATION_____ April 2020_____

NAME AND VOLUME OF JOURNAL (where appropriate)

____PLoS Med. 2020 Apr;17(4):e1003100.

PUBLISHER (for book, chapter or monograph)

EDITORS (chapter only)

ISBN (where appropriate)

If the work has not been published but has been accepted for publication please attach a statement from the Editor or Publisher which confirms the intention to publish the work.

NAMES OF JOINT AUTHORS INSTITUTION

1. Dawn Craig - Newcastle University

2. Robert Barker - Newcastle University

3. Gemma Spiers - Newcastle University

4. Daniel Stow - Newcastle University (now at QMUL)

5. Quentin Anstee - Newcastle University

6. Barbara Hanratty - Newcastle University

CONTRIBUTION OF THE CANDIDATE TO THIS WORK (%)

Design of investigation _____90%_____

Conduct of research _____70%_____

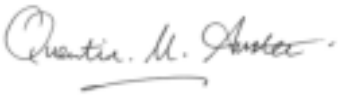
Analysis of outcome _____90%___

Preparation for publication _____90%_____

TOTAL ____85%_____ *(To be an average of, or at least consistent with, the above figures)*

This statement should be endorsed by all of the co-authors.

I confirm that the above is a true estimate of the candidate's contribution to this work.

Signature 1 __  _____

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_____ Signature 4

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A candidate should submit a separate form for each jointly authored work which is submitted for the degree.

TITLE OF PUBLICATION (article, book, chapter, monograph)

Does moderate alcohol consumption accelerate the progression of liver disease in NAFLD? A systematic review and narrative synthesis

DATE OF PUBLICATION_____ January 2022_____ NAME

AND VOLUME OF JOURNAL (where appropriate)

___BMJ Open. 2022 Jan 4;12(1):e049767.

_____ PUBLISHER (for book, chapter or monograph)

EDITORS (chapter only)

ISBN (where appropriate)

If the work has not been published but has been accepted for publication please attach a statement from the Editor or Publisher which confirms the intention to publish the work.

NAMES OF JOINT AUTHORS INSTITUTION

1. Hannah O'Keefe Newcastle University

2. Dawn Craig - Newcastle University

3. Daniel Stow - Newcastle University (now at QMUL)_____

4. Barbara Hanratty - Newcastle University

5. Quentin Anstee - Newcastle University

CONTRIBUTION OF THE CANDIDATE TO THIS WORK (%)

Design of investigation _____90%_____

Conduct of research _____70%_____

Analysis of outcome _____90%_____

Preparation for publication ____90%_____

TOTAL ____85%_____ *(To be an average of, or at least consistent with, the above figures)*

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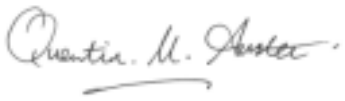
Signature 1____ 

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A candidate should submit a separate form for each jointly authored work which is submitted for the degree.

TITLE OF PUBLICATION (article, book, chapter, monograph)

The pathway to better primary care for chronic liver disease

DATE OF PUBLICATION

April 2021

NAME AND VOLUME OF JOURNAL (where appropriate)

Br J Gen Pract. 2021 Apr 1 ;71(705):180–2.

PUBLISHER (for book, chapter or monograph)

EDITORS (chapter only)

ISBN (where appropriate)

If the work has not been published but has been accepted for publication please attach a statement from the Editor or Publisher which confirms the intention to publish the work.

NAMES OF JOINT AUTHORS INSTITUTION

1. Stuart McPherson - Newcastle University

2. Quentin Anstee - Newcastle University

_____

3. Barbara Hanratty - Newcastle University

_____

4.

_____

CONTRIBUTION OF THE CANDIDATE TO THIS WORK (%)

Design of investigation _____90%_____

Conduct of research _____90%_____

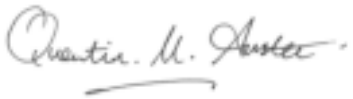
Analysis of outcome _____90%_____

Preparation for publication _____90%_____

TOTAL _____90%_____ *(To be an average of, or at least consistent with, the above figures)*

This statement should be endorsed by all of the co-authors.

I confirm that the above is a true estimate of the candidate's contribution to this work.

Signature 1 ___  _____

Signature_ 

_____ Signature 3

_____ Signature 4

_____

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CO-AUTHORSHIP FORM

This form must accompany any submission of a joint authored publication for the degree of Doctor of Philosophy on the basis of published work.

A candidate should submit a separate form for each jointly authored work which is submitted for the degree.

TITLE OF PUBLICATION (article, book, chapter, monograph)

Engagement with community liver disease management across the UK: a cross-sectional survey

DATE OF PUBLICATION July 2021

NAME AND VOLUME OF JOURNAL (where appropriate)

BJGP Open. 2021 Jul 5; BJGPO.2021.0085.

PUBLISHER (for book, chapter or monograph)

EDITORS (chapter only)

ISBN (where appropriate)

If the work has not been published but has been accepted for publication please attach a statement from the Editor or Publisher which confirms the intention to publish the work.

NAMES OF JOINT AUTHORS INSTITUTION

1. Jonathan Worsfold - British Liver Trust

2. Vanessa Hebditch - British Liver Trust

3. Stephen Ryder - Nottingham University Hospitals NHS trust/British Liver Trust

4.

CONTRIBUTION OF THE CANDIDATE TO THIS WORK (%)

Design of investigation ____70%_____

Conduct of research _____50%_____

Analysis of outcome _____90%_____

Preparation for publication ___90%_____

TOTAL _____75%____ *(To be an average of, or at least consistent with, the above figures)*

This statement should be endorsed by all of the co-authors.

I confirm that the above is a true estimate of the candidate's contribution to this work.

Signature 1 ____  _____ Signature 2

_____ Signature 3

_____ Signature 4

_____

SUBMISSION BY STAFF CANDIDATES FOR THE DEGREE OF PHD BY PUBLISHED WORK

CO-AUTHORSHIP FORM

This form must accompany any submission of a joint authored publication for the degree of Doctor of Philosophy on the basis of published work.

A candidate should submit a separate form for each jointly authored work which is submitted for the degree.

TITLE OF PUBLICATION (article, book, chapter, monograph)

GPs' experiences and perceptions of early detection of liver disease:a qualitative study in primary care

DATE OF PUBLICATION_____November 2018_____

NAME AND VOLUME OF JOURNAL (where appropriate)

Br J Gen Pract. 2018 Nov;68(676):e743–9.

PUBLISHER (for book, chapter or monograph)

EDITORS (chapter only)

ISBN (where appropriate)

If the work has not been published but has been accepted for publication please attach a statement from the Editor or Publisher which confirms the intention to publish the work.

NAMES OF JOINT AUTHORS INSTITUTION

1. Holly Standing - newcastle university (now working for emis health)
2. James Orr - newcastle upon tyne NHS trust (now at Bristol NHS)
3. Catherine Exley - newcastle university
4. Mark Hudson - newcastle upon tyne NHS trust (now retired)
5. Eileen Kaner - newcastle university
6. Barbara Hanratty - newcastle university

CONTRIBUTION OF THE CANDIDATE TO THIS WORK (%)

Design of investigation _____20%_____

Conduct of research _____20%_____

Analysis of outcome _____50%_____

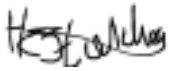
Preparation for publication _80%_____

TOTAL _____40 %___ *(To be an average of, or at least consistent with, the above figures)*

This statement should be endorsed by all of the co-authors.

I confirm that the above is a true estimate of the candidate's contribution to this work.

Signature 1 _____



Signature 2 

_____ Signature 3

_____ Signature 4

_____

SUBMISSION BY STAFF CANDIDATES FOR THE DEGREE OF PHD BY PUBLISHED WORK

CO-AUTHORSHIP FORM

This form must accompany any submission of a joint authored publication for the degree of Doctor of Philosophy on the basis of published work.

A candidate should submit a separate form for each jointly authored work which is submitted for the degree.

TITLE OF PUBLICATION (article, book, chapter, monograph)

_Liver disease management as routine work in primary care:A qualitative interview study to guide implementation_____

DATE OF PUBLICATION____December 2022_____ _____

NAME AND VOLUME OF JOURNAL (where appropriate)

Br J Gen Pract. 2022 Dec;72(725):e916–23.

PUBLISHER (for book, chapter or monograph)

EDITORS (chapter only)

ISBN (where appropriate)

If the work has not been published but has been accepted for publication please attach a statement from the Editor or Publisher which confirms the intention to publish the work.

NAMES OF JOINT AUTHORS INSTITUTION

1. Tom Sanders - University of Northumbria
2. Barbara Hanratty - Newcastle University
3.

4.

CONTRIBUTION OF THE CANDIDATE TO THIS WORK (%)

Design of investigation _____90%_____

Conduct of research _____100%_____

Analysis of outcome _____80%_____

Preparation for publication ____90% _____

TOTAL _____90%_____ *(To be an average of, or at least consistent with, the above figures)*

This statement should be endorsed by all of the co-authors.

I confirm that the above is a true estimate of the candidate's contribution to this work.

Signature 1_____  __ _____

Signature 2 ___ 

_____ Signature 3

_____ Signature 4

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