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Primary Care and Population Sciences

Coffee Consumption and Liver Health

Volume 1 of 1

by

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Abstract

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Beneficial associations between coffee drinking and a range of liver outcomes have been consistently reported in observational research, yet no randomised controlled trial has been conducted to investigate whether drinking more coffee might reduce the risk of progression of Non-Alcoholic Fatty Liver Disease (NAFLD). NAFLD is an umbrella term for a pathological pathway that includes steatosis, steatohepatitis, fibrosis, cirrhosis, and hepatocellular carcinoma, where no other aetiology is identified such as alcohol or viral hepatitis. NAFLD is an important public health issue with a general population prevalence of approximately 25% that has risen in parallel with that of obesity, and as such represents a significant burden to individuals and health systems. NAFLD has few treatment options and current best advice is to lose weight through healthy diet and exercise. If coffee was shown to have benefit in reducing the risk of NAFLD progression it would be a valuable addition to the current management of the condition.

The methodological approach of a randomised controlled study could be shaped by addressing a number of current knowledge gaps. Firstly, could increasing coffee intake cause additional non-liver harm in people. To address this issue an umbrella review, or review of reviews, was conducted to draw together the vast amount of existing research between coffee intake and multiple health outcomes. Reassuringly, outside of pregnancy, drinking coffee was more frequently associated with benefit than harm. For important generic outcomes such as all-cause mortality, cardiovascular mortality, and incident cardiovascular disease, maximum relative risk reduction was associated with intakes of 3-5 cups a day. Some harmful associations, such as between coffee drinking and lung cancer, were nullified by adequate adjustment for smoking, known to be an important confounder. Liver outcomes consistently had the largest magnitude of beneficial associations with coffee drinking.

Secondly, in observational research, ascertainment of coffee intake is usually measured in cups a day. This is a heterogeneous measure because of different preparation methods, cup sizes, coffee beans, and roast types, resulting in the risk of misclassification. To overcome this limitation the next stage of the research aimed to create a coffee unit measure, similar in concept to alcohol units, that took preparation method and cup size into account. The unit measure, where 1 coffee unit was equivalent to a 227mL cup of instant coffee, was then applied to a representative UK population using data from the National Diet and Nutrition Survey, and the proportion of misclassified intake, when not accounting for preparation type and cup size was derived. Overall, approximately 1 in 4 participants had misclassified intake, largely under or over estimated by one cup a day. This effect of 25% misclassification of coffee intake in existing research is of uncertain significance, but would generally be non-differential, and therefore more likely to dilute risk estimates of both benefit and harm. The coffee unit measure could be applied to a future experimental study to better quantify coffee intake or allow increases in consumption across preferred preparation types.

Coffee preparation preferences were explored as part of the final element of the research, which was a mixed-methods study designed to explore patterns of coffee consumption in a secondary care population of people with NAFLD, their views about drinking more coffee, and acceptability of a randomised controlled trial in which drinking more coffee was the intervention. The mixed method study included an initial qualitative phase of 17 semi-structured interviews that were used to inform the final design of a questionnaire to explore the same phenomenon in a stratified sample of 393 people with NAFLD recruited from three NHS secondary care sites. In the survey, which was stratified across three liver stiffness groups (<7 KPa, 7-13 KPa, and >13 KPa), 78% of respondents were current coffee drinkers, and 22% non-coffee drinkers. Median coffee consumption was 2 cups a day (interquartile range 1 to 3 cups). The proportion of coffee drinkers reduced as liver stiffness increased but not the median daily cup intake. Nearly half of non-coffee drinkers thought they would be able to start drinking it, and 85% of those drinking <4 cups a day thought they would be able to drink an additional 2 cups a day. These proportions reduced to 38% and 66% respectively when considering those who also expressed an interest, albeit hypothetically, in becoming involved in a randomised controlled trial. In this group of participants, acceptable options for increasing coffee intake included 71% for drinking their own coffee at their own expense, 32% being supplied instant coffee, 27% being given a monetary allowance towards the extra coffee, and 15% being supplied ground coffee. Other aspects of a future experimental study including randomisation, and blood and imaging tests were generally considered acceptable. Importantly this data suggests that recruiting people with NAFLD into a future experimental study would be possible from an NHS secondary care setting. Arguably, now is the time for such a study, in the context

of the huge burden of NAFLD, the lack of effective treatments, and the potential coffee has to offer benefit.

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Research Thesis: Declaration of Authorship

Print name:	Robin Geoffrey Poole

Title of thesis:	Coffee Consumption and Liver Health

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

I confirm that:

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

Poole R, Kennedy OJ, Roderick P, Fallowfield JA, Hayes PC, Parkes J. Coffee consumption and health: umbrella review of meta-analyses of multiple health outcomes. Bmj. 2017 Nov 22;359:j5024.

Poole R, Ewings S, Parkes J*, et al*. Misclassification of coffee consumption data and the development of a standardised coffee unit measure. *BMJ Nutrition, Prevention & Health* 2019;bmjnph-2018-000013. doi: 10.1136/bmjnph-2018-000013

Poole R, Parkes J, Cook C, *et al*. Feasibility of increasing coffee consumption in people with non-alcoholic fatty liver disease: a multi-centre, mixed methods study. *British Association of the Study of the Liver Conference Abstract*. September 2019. Glasgow.

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Definitions and Abbreviations

ACETYL-CoA	Acetyl-Coenzyme A
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AMPK	Adenosine Monophosphate-activated Protein Kinase
AMSTAR	A measurement tool to assess systematic reviews
AP-1	Activator Protein 1
ASSALD	American Association for the Study of Liver Disease
AST	Aspartate Aminotransferase
AUDIT-C	Alcohol Use Disorders Identification Test
BAFLD	Both Alcohol and Fatty Liver Disease
BMI	Body Mass Index
ChREBP	Carbohydrate Regulatory Element Binding Protein
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CTGF	Connective Tissue Growth Factor
EASL	European Association for the Study of the Liver
ELF	Enhanced Liver Fibrosis Test
FFA	Free Fatty Acids
GGT	Gamma-glutamyl-transpeptidase
GRADE	Grading of recommendations, assessments, development and evaluation
GST	Glutathione S-transferase
HCC	Hepatocellular Carcinoma
HDL	High Density Lipoproteins
HSC	Hepatic Stellate Cells
ICD-9	International Classification of Disease – 9th Revision
IL	Interleukin
JAK/STAT	Janus Kinase/Signal Transducers and Activators of Transcription
LDL	Low Density Lipoproteins
MAPK	Mitogen-Activated Protein Kinase
MCP-1	Monocyte Chemoattractant Protein 1
MMP	Matrix Metalloproteinases
MR	Mendelian Randomisation
NAFLD	Non-Alcoholic Fatty Liver Disease
NASH	Non-alcoholic SteatoHepatitis
NDNS	National Diet and Nutrition Survey
NF-κB	Nuclear Factor kappa-light-chain-enhancer of activated B cells
NOX4	Nicotinamide Adenine Dinucleotide Phosphate Oxidase 4
NRF2	Nuclear factor erythroid 2-Related Factor 2
PPAR α	Peroxisome Proliferator Activated Receptor α
PPAR γ	Peroxisome Proliferator-Activated Receptor γ
SMAD	Mothers Against Decapentaplegic Homolog
SNP	Single Nucleotide Polymorphism
SREBP-1c	Sterol Regulatory Element Binding Protein 1c
T2DM	Type 2 Diabetes Mellitus
TGF-β	Transforming Growth Factor β
TIMP	Tissue Inhibitors of MMP
TLR4	Toll-like receptor 4 (TLR4)
TNF- α	Tissue Necrosis Factor α
UK	United Kingdom

VLDL	Very Low Density Lipoproteins
α-SMA	Alpha Smooth Muscle Actin

Chapter 1: Background and aims

1.1 Liver disease

Unlike many long-term conditions, mortality from chronic liver disease (CLD) in the UK has increased over time[1]. This is represented graphically in Figure 1. The main drivers for chronic liver disease are alcohol, obesity and viral hepatitis with evidence of interaction between risk factors[2]. The huge burden on individuals and health systems due to chronic liver disease, coupled with the high prevalence of these preventable risk factors, position chronic liver disease as a major public health issue[3]. The importance is further highlighted by the fact that early stages of liver disease are frequently asymptomatic, patients present late with advanced disease, and die young as a result. This leads to a high level of premature mortality and places chronic liver disease as the third leading cause of premature mortality after ischaemic heart disease and self-harm[1].

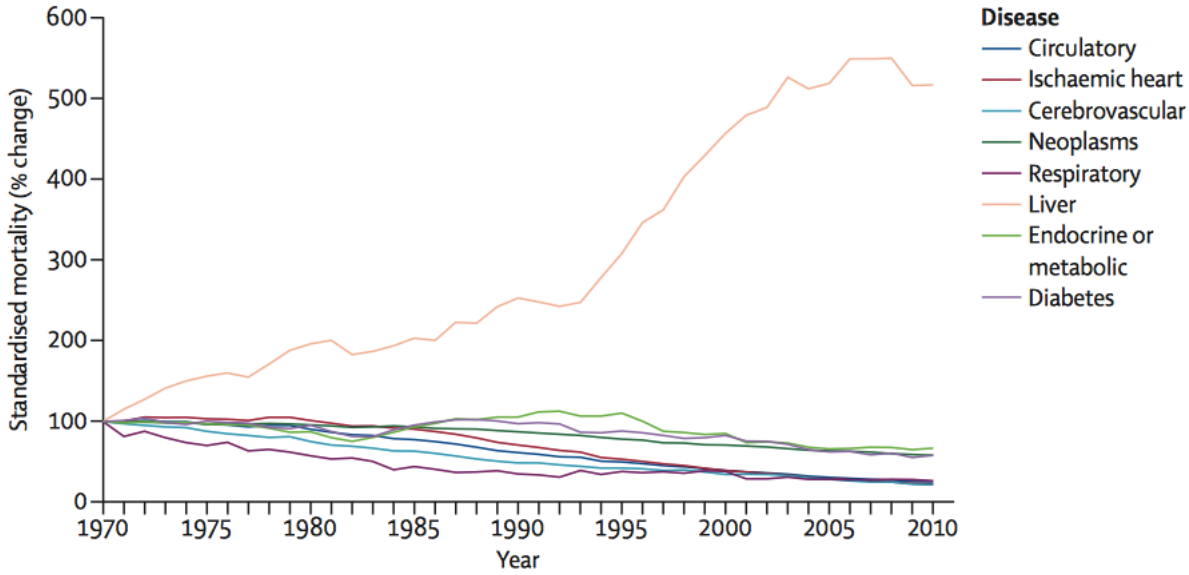


Figure 1: Standardised mortality rates comparing liver disease to other chronic diseases UK[i]

[i] Reproduced from reference [1]

1.1.1 Non-alcoholic Fatty Liver Disease

The most prevalent CLD globally is Non-alcoholic Fatty Liver Disease (NAFLD)[4]. NAFLD is broadly defined as the accumulation of fat in the liver cells in the absence of other aetiologies including metabolic conditions, alcohol, and viral hepatitis. In the last twenty years, the prevalence of NAFLD has increased in parallel with the rise in obesity and type 2 diabetes (T2DM), two of its main risk factors, both of which are predicted to continue to rise in prevalence over the next 20 years[5]. Globally, the prevalence of NAFLD in the population is believed to be in the order of 20-25%, increasing to 70% in people with type II diabetes mellitus[6]. NAFLD leads to 5,000 hospital admissions and 700 deaths each year in England alone[7], and is now the indication for a substantial proportion of liver transplants[8]. Few effective treatment options currently exist for NAFLD, and the main management strategy is encouraging weight loss through healthy diet and exercise, known to be challenging for individuals.

Inherent in the definition, NAFLD is fatty liver disease that is NOT pathologically associated with alcohol consumption. This does not mean that a person is completely abstinent from all alcohol consumption and the current cut offs vary between diagnostic criteria produced by different organisations. For example the American Association for the Study of Liver Diseases (AASLD) cut offs are <21 units alcohol a week for men and <14 for women, consumed over the previous two year period[9] and the European Association for the Study of the Liver (EASL) cut offs are <20g per day for women (2.5 units) and <30g per day for men (3.75 units)[10]. The reality is obesity and alcohol will both contribute to the occurrence of NAFLD[6], although there is some evidence that increasing intake of alcohol up to a maximum of 13 units per week is associated with a lower risk of progression[11]. It should also be noted that it is possible to be metabolically unhealthy (eg. dyslipidaemia, high HbA_{1c}, higher waist circumference) with a normal Body Mass Index (BMI) and still have NAFLD[12].

NAFLD is an umbrella term that encompasses a range of liver pathology that share a common pathway from simple steatosis (fatty liver), steatohepatitis (inflamed fatty liver), fibrosis (early scarring), cirrhosis (more significant scarring) and hepatocellular carcinoma (HCC)[13]. Most people with simple steatosis do not progress to the next stage of the disease but due to its high prevalence, even a small proportion of people with progressive disease equates to a high disease burden. The first stage of progression is called Non-alcoholic steatohepatitis (NASH), defined by having fat accumulation plus inflammation with hepatocyte injury (ballooning)[13], that can lead to fibrosis, cirrhosis and HCC. This pathway is represented in Figure 2. The causes for NAFLD to progress to NASH are not

fully understood but may be linked to insulin resistance and metabolic syndrome, with oxidative stress and cytokines being important contributors[14]. The pathophysiology is discussed further in a later section. Cardiovascular disease is an additional risk in people with NAFLD and accompanies type II diabetes, dyslipidaemia, and hypertension, such that cardiovascular mortality is the leading overall cause of death in people with NAFLD[15].

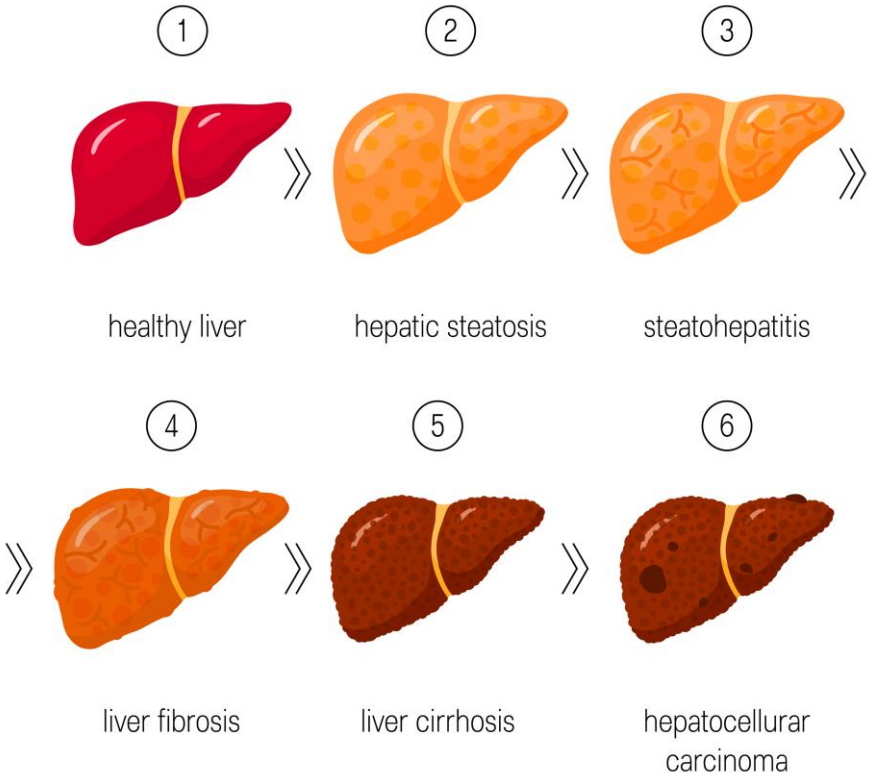


Figure 2: Pathway from healthy liver to hepatocellular carcinoma[i]

1.1.2 NAFLD Treatment options

Current treatment options for NAFLD and disease progression are limited. There are a few pharmacological agents that have marginal benefit in managing the metabolic components of NAFLD and are indicated for progressive NASH or NASH with higher risk for progression such as being older, having diabetes or metabolic syndrome[13]. In all cases

[i] Standard license purchased from Shutterstock.com

lifestyle behaviour changes are the principal treatment option. There is evidence that weight loss due to diet and physical activity can reduce liver adiposity as well as improve markers of glycaemic function[16]. However, sustained weight reduction following a dietary phase is difficult and for some people, losing weight represents a considerable challenge.

1.1.3 NAFLD and Coffee

Associations between coffee consumption and markers of liver health have been subject to research for the last three decades. There appears to be a beneficial association between coffee consumption and lower risk of liver fibrosis, cirrhosis and HCC, although firm evidence for causation remains elusive. Interventional studies are needed to better understand whether coffee can beneficially influence the natural progression of the NAFLD pathological pathway. If evidence suggests coffee can be beneficial in reducing risk of progression in NAFLD it could be a useful addition to the limited treatment options for people with established liver disease, being low cost and easily accessible. It may also lead to wider public health recommendations regarding coffee as a healthful part of the diet, especially for liver health, since the wider population is likely to include a large proportion of subclinical NAFLD. This is of course conjecture, since firm causative evidence for the benefit of coffee in NAFLD does not yet exist.

This thesis describes three separate research studies with the overarching aim of bridging the knowledge gap between existing observational evidence for the apparent benefit of coffee consumption in liver disease, and an interventional study in which coffee is tested as a treatment in people with NAFLD. This first chapter will explain the nature of coffee and its chemistry, explain the basic anatomy and physiology of the liver, summarise existing research investigating coffee consumption and chronic liver disease, and discuss biological plausibility for an effect. The chapter will conclude by describing the aims of the research questions contained within the thesis, and the broad methods used to answer them.

1.2 Coffee

Coffee is ubiquitous in modern societies and is most frequently consumed as a hot beverage. Worldwide, more than two billion cups of coffee are consumed every day and

includes 55 million cups in the UK[17]. Coffee originates from a plant belonging to the genus Coffea of the Rubiaceae family (Figure 3) that was discovered over a thousand years ago in Ethiopia. Since then, cultivation and consumption has spread globally with *Coffea arabica,* and *Coffea canephora* (Robusta), being the main species of coffee producing plants that supply the world with coffee beans[18](Figure 3). The coffee cherries are harvested as green coffee beans, dried, roasted and brewed by a variety of methods which extract aromatic compounds that result in a cup of coffee[19]. Coffee is the leading export commodity in developing countries after oil and globally, millions of people rely on its production for their livelihood[18,20].

Figure 3: Coffea Arabica Plant[i]

Figure 4: Arabica and Robusta coffee beans[ii]

The type of bean (Arabica versus Robusta as in Figure 4), degree of roasting and preparation method (including coffee grind setting and brew type), will all have an

[i] Coffea Arabica plant image - Wikimedia commons image
[ii] Coffee Arabica/Robusta bean image - standard licence purchased from Shutterstock.com

influence on the chemical composition of the final cup[21–23]. Preparation methods will be discussed in more detail in chapter 3.

1.2.1 The chemistry of coffee

Coffee undergoes a chemical metamorphosis between the unroasted green bean and the final product that ends up in the cup. Green coffee beans consist of a mixture of complex carbohydrates, sugars, fibre, lipids, vitamins, minerals and nitrogen containing molecules[24]. These include protein, free amino acids, and the alkaloids caffeine and trigonelline[18]. They also contain phenols, such as chlorogenic acid[25], which undergo transformation during the roasting process and which, along with trigonelline, ketones and aldehydes, are responsible for the aroma and taste of the final product[19]. During roasting, fibre-like structures called melanoidins are produced by the Maillard reaction[18] between carbohydrate and protein components of the coffee which are responsible for giving coffee its rich brown colouration. The lipid component of coffee contributes significantly to the 'mouthfeel' of the final drink[26] of which 20% is comprised of diterpenes, mainly cafestol and kahweol. Broad beneficial biological effects of coffee constituents are shown in Table 1.

Table 1: Coffee compounds and broad beneficial biological effects

Compound	Antioxidant	Anti-cancer	Anti-fibrotic	Other actions
Caffeine	✔	✔	✔	Increase sympathetic activity
Chlorogenic acid	✔	✔	✔	
Trigonelline		✔		Neuroprotective, anti-microbial, hypoglycaemic, phyto-oestrogen
Diterpenes		✔	✔	Hyperlipidaemic
Melanoidins	✔	✔		Dietary fibre, anti-microbial

Chlorogenic acids are a major source of dietary antioxidants[18]. Caffeine (1,3,7-trimethylxanthine) also has significant antioxidant activity, and is the most recognised and researched component of coffee, known for its central nervous and cardiovascular stimulating properties[18]. The diterpenes are known to increase blood cholesterol but also have anti-carcinogenic properties[27]. In addition to the bean, roast, grind and preparation

method, an individual's genotype and gut microbiome will affect the bioavailability and type of coffee metabolites to which that individual is finally exposed[28]. The biological plausibility of coffee in liver health is discussed in more detail in section 1.6.

1.3 Liver structure and function

The liver is the largest of the internal organs of the human body and is situated in the upper-right aspect of the abdominal cavity as shown in Figure 5. It has a rich blood supply with oxygenated blood flowing in via the hepatic artery and nutrient rich blood from the portal hepatic vein which drains most of the gastrointestinal tract and spleen[29,30]. The liver has two lobes and each is divided into eight segments, which in turn are subdivided into 1000 lobules each, that are connected to small ducts that converge to form the common hepatic duct. The common hepatic duct becomes the common bile duct and transports bile from the liver into the gall bladder and small intestine. The bile contains the metabolic and detoxification breakdown products, which are then reabsorbed, further metabolised by gut microbiota, or excreted from the body as faeces. Other outputs from the liver reach the central hepatic veins via sinusoids which are lined by specialised endothelial cells, phagocytic cells (Kupffer's cells) and fat storage cells (Ito cells) as shown in Figure 6. The sinusoids are separated by sheets of liver cells called hepatocytes[29].

Figure 5: Anatomical position of the liver[i]

[i] Anatomical position of the liver image – standard licence purchased from Shutterstock.com

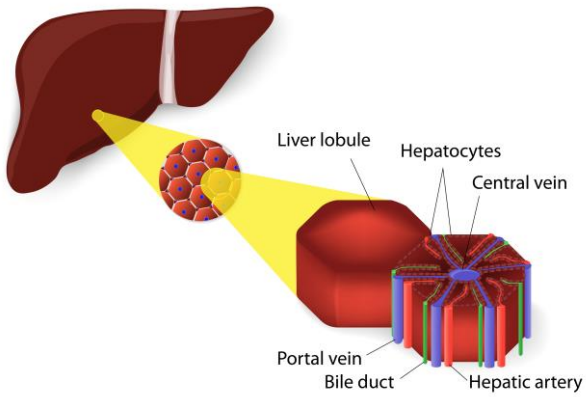


Figure 6: Anatomy of a liver lobule[i]

This anatomy corresponds to the important functions of the liver in protein, carbohydrate and lipid metabolism[29,30]. The liver synthesises most proteins within the body such as albumin, which maintains intravascular oncotic pressure and transports water-insoluble substances. It also synthesises coagulation factors that are vital for normal blood clotting function. It metabolises amino acids via transamination and oxidative transamination. This produces ammonia that is later excreted by the kidneys as urea. The liver can release glucose from stored glycogen or synthesise new glucose to maintain circulating blood glucose. Glucose is the fuel for every cell in the body and helping to maintain glucose homeostasis is a vital function of the liver. Fats are attached to proteins called lipoproteins for transportation in the blood and these are also synthesised by the liver along with cholesterol and triglycerides. Further functions of the liver include deactivating and breaking down hormones including insulin, glucagon, and oestrogens. It also metabolises drugs including caffeine and alcohol. The liver can also sieve bacteria and antigens that arrive from the gastrointestinal tract via the hepatic portal vein and remove them via the Kupffer's cells.

1.4 Liver biopsy

A liver biopsy is a procedure used to remove a small piece of liver tissue which can then be examined by a laboratory. A microscope is used to look for presence and severity of damage or disease. Commonly the liver biopsy is conducted with the patient awake and a

[i] Anatomy of a liver lobule image – standard licence purchased from Shutterstock.com

needle is inserted from outside the abdominal wall into the liver to remove the liver tissue, often using ultrasound or other imaging to make sure the needle is in the right place. The main risks of the procedure include bleeding, pain, infection, damage to other organs including a collapsed lung. Liver biopsy is recognised as the 'gold standard' for the assessment and quantification of liver pathology such as liver fibrosis but is not well accepted by patients. This has led to interest in non-invasive markers of liver function as more acceptable alternatives to liver biopsy.

1.5 Non-invasive markers of liver function

1.5.1 Liver enzymes

Liver enzymes are proteins in the liver that help to speed up certain chemical processes. Liver enzymes do not give any quantitative indication of functional capacity of the liver but when abnormally raised can point towards severity and type of liver damage and are non-invasive[30], requiring only a blood sample rather than a liver biopsy. Serum aminotransferases are a measure of the integrity of the hepatocytes. Alanine aminotransferase (ALT) is released from the cytosol of a damaged hepatocyte. Aspartate aminotransferase (AST), becomes raised with further cellular damage and is contained within the mitochondria. AST is not so specific to the liver and is elevated in kidney, heart and skeletal muscle damage. Gamma-glutamyl-transpeptidase (GGT) is a very sensitive index of liver pathology and can increase with alcohol ingestion in the absence of liver damage and will also rise whenever there is blockage to bile flow (cholestasis) along with Alkaline Phosphatase (ALP) and bilirubin[30]. ALP is also not specific to the liver and will also elevate with bone and intestinal pathologies.

1.5.2 NAFLD and liver enzymes

NAFLD is the most common cause of abnormal liver function tests although in most cases NAFLD runs a benign course and there will be normal liver enzymes[6]. An increase in ALT relative to AST, can suggest hepatic steatosis from NAFLD, whereas alcohol related fatty liver disease often manifests as a higher AST relative to ALT. However as steatosis becomes more advanced in NAFLD, both the AST to ALT ratio increases in conjunction

with GGT. ALT and GGT, but not AST, have associations with fatty liver ascertained by ultrasound scanning or magnetic resonance imaging[6].

More recently other biochemical markers of liver fibrosis have been developed such as the Enhanced Liver Fibrosis (ELF) test [31]. The ELF test has a high sensitivity and specificity for identifying liver fibrosis in a clinical setting[32] when compared to the gold standard of liver biopsy.

1.5.3 Transient elastography

Liver stiffness is another non-invasive measure of liver fibrosis and cirrhosis. It can be measured relatively simply using ultrasound transient elastography, such as Fibroscan, and measures the speed of propagation of a low frequency elastic shear wave sent through a probe applied between the 9th and 11th intercostal space over the liver[33]. The wave moves faster as the liver becomes stiffer. The procedure can take place in an outpatient setting, taking only a few minutes to complete, and the results are available immediately. The results are measured in kilopascals (kPa) and a normal value is approximately 5 kPa. Although Fibroscan has high inter- and intra-observer agreement, there are concerns regarding its reliability, especially when measured in patients with obesity. Liver inflammation can also affect the liver stiffness measurement. Additionally, transient elastography may be more accurate at diagnosing cirrhosis than advanced fibrosis, and has a higher negative predictive value than positive predictive value such that it is better at ruling out than ruling in disease[33].

1.6 Coffee consumption and liver health

This section provides background on coffee consumption in relation to liver enzymes, steatosis, fibrosis, cirrhosis and HCC.

1.6.1 Coffee consumption and liver enzyme changes

A summary of the studies investigating coffee consumption and liver enzymes is shown in Table 2.

Table 2: Coffee consumption and liver enzyme studies

Year	Author	Setting	Study Design	No. of subjects	Effect	Main findings
1990	Nilssen[34]	Norway	C/S	21782	↓	Strong inverse correlation between coffee drinking and GGT
1993	Casiglia[35]	Italy	C/S	2240	↓	AST/ALT/GGT consistently lower in coffee drinkers
1994	Kono[36]	Japan	C/S	2494	↓	Coffee independently inversely associated with GGT
1998	Tanaka[37]	Japan	C/S	12687	↓	AST/ALT/GGT consistently lower in coffee drinkers; not green tea
1998	Aubin[38]	France	C/S	160	↓	Coffee but not caffeine correlated with lower AST/GGT
1999	Nakanishi[39]	Japan	CO	1221	↓	Coffee drinking independently inversely associated with rises in AST/ALT
1999	Honjo[40]	Japan	C/S	6095	↓	GGT consistently lower in coffee drinkers
2000	Nakanishi[41]	Japan	C/S	1353	↓	Coffee independently inversely associated with GGT
2001	Honjo[42]	Japan	C/S	7000	↓	AST/ALT lower in coffee drinkers
2005	Ruhl[43]	US	C/S	5944	↓	High risk liver population ALT lower in higher coffee & caffeine drinkers
2010	Ikeda[44]	Japan	C/S	12020	↓	Inverse association between coffee drinking and ALT especially in men
2012	Jang[45]	Korea	C/S	500	↓	Coffee drinking associated with lower AST, total protein and albumin
2013	Danielsson[46]	Finland	C/S	18899	↓	Coffee mitigates alcohol related rise in GGT
2014	Xiao[47]	US	C/S	27793	↓	Total coffee associated with lower ALT/AST/ALP/GGT

C/S: Cross-Sectional; CO: Cohort

Coffee consumption and associations with liver health were first investigated in the early 1990's when the third Tromsø study population was conducted to determine population determinants of GGT[34]. The Tromsø studies had been designed to combat the high level of cardiovascular mortality in Norway because 20% of Norwegian men died from myocardial infarction before the age of 75. GGT was recognised as being associated with alcohol intake and used in clinical practice to monitor alcohol-related damage to the liver but little was known about its epidemiology. The third Tromsø study population presented an opportunity to understand more about GGT in a cross-sectional analysis of over 20,000 men and women. Alcohol, body mass index (BMI) and serum cholesterol were all found to be positively associated with GGT whilst coffee drinking had significant negative associations. Publication of this evidence lead to similar observational investigations being conducted in other population groups including Italy[35], France[38], Finland[46], Korea[45], Japan[36,37,41,42,44] and the US[43,47]. All bar one of these investigations followed a cross-sectional design, accounted for a varying, but inconsistent, number of potential confounders, and all confirmed negative associations between coffee consumption and lower liver enzyme activity. They also found negative associations between coffee consumption and other liver enzymes or markers of liver function, such as ALT, AST, ALP, bilirubin and total protein. In most, but not all studies, the associations were found to be independent of the confounding effects of alcohol consumption, smoking and BMI.

Coffee consumption also appeared to mitigate detrimental effects of increasing alcohol intake on liver enzymes suggesting an interaction of the effects of coffee and alcohol. Some studies suggested that the association of coffee with lower liver enzymes was not seen in those that were past or never users of alcohol[37,42] suggesting that coffee might have a protective effect only when another damaging aetiology was present. This is supported by a US based study that showed the ALT lowering associations of coffee consumption extended to those with risk factors for liver pathology (alcohol use >2 units/day, viral hepatitis, iron overload, impaired glucose tolerance, or overweight). The association was seen with both coffee and caffeine exposure[43] suggesting caffeine had an important role in the protective effect.

Most studies concluded that coffee contained a component that targeted liver function, and thus liver enzyme activity, but were not able to suggest which component of coffee this might be. They were also unable to hypothesise as to whether coffee consumption lowered liver enzyme activity or prevented elevation. Studies that also assessed tea consumption in relation to levels of liver enzymes found no associations[36,37]. Due to the lower concentration of caffeine in tea, the threshold for the effect on liver enzymes may

not be reached within usual consumption patterns, or caffeine may require other components of coffee, such as the polyphenols, to exert an effect.

A consistent limitation of the observations between coffee consumption and liver enzymes were the varied ascertainment of coffee drinking and the lack of detailed information regarding preparation method, strength and cup size. One study suggested the inverse associations between coffee consumption and levels of liver enzymes were more potent in those drinking instant coffee compared with filtered coffee[40] but both had an effect. Lack of detailed information about coffee intake is a recurrent issue of most observational studies and is explored in more detail in chapter 3. However, the consistent findings across different populations and settings, with different coffee cultures and preparation types, suggest that the inverse associations of coffee consumption with levels of liver enzymes are unlikely to result from misclassification of exposure. Most of the cross-sectional studies excluded subjects with abnormally high liver enzymes to reduce the risk of reverse causality caused by subjects changing their coffee drinking patterns as a result of an awareness, or symptoms, of liver pathology. However, no information on co-morbidities or medication use, which could also change coffee consumption patterns and affect liver enzymes, were included.

During the early years of these investigations a small number of interventional trials involving a limited number of participants also took place in Norway and Holland[48–50]. These were designed to investigate the association of drinking unfiltered coffee on cholesterol but also measured liver enzyme changes. These studies concluded that the lipid component of coffee and specifically the non-triacylglyercol fatty acids, cafestol and kahweol, caused the elevations in cholesterol. Acute consumption of unfiltered coffee was also found to lower serum GGT but unlike the observational study findings, increased ALT, although it remained within the normal range[48]. On stopping coffee drinking the GGT would temporarily rise and exceed the baseline readings before both enzymes returning to normal at 12 months. Neither changes in cholesterol, nor the changes in liver enzymes, were found to occur when filtered coffee was used instead. Filtered coffee contains much less cafestol and kahweol which is trapped by the filter paper. Further experimental studies suggested that different biochemical pathways were likely to be involved in coffee-related changes in cholesterol and ALT[50].

Considered together it appears that there is consistent evidence that chronic coffee consumption is inversely associated with levels of liver enzymes, but that short-term exposure may lead to transient rises in ALT. The evidence is mixed as to whether the associations are independent or modified by other risk factors, such as alcohol and

smoking. The limitations of cross-sectional studies in temporality of cause and effect, and the risks of insufficient adjustment for confounding factors should also be considered when interpreting this evidence.

1.6.2 Coffee consumption and steatosis

A summary of the studies investigating coffee consumption and steatosis are presented in Table 3.

Table 3: Coffee consumption and liver steatosis studies

Year	Author	Setting	Study Design	No. of cases/ controls or total subjects	Effect	Main findings
2010	Catalano[51]	Italy	C/S	310	↓	Greater espresso coffee consumption associated with lower liver brightness score (less steatosis); obesity and insulin resistance positively associated with steatosis. Espresso consumption not significantly associated with insulin resistance. Only espresso coffee and only subjects with normal ALT.
2011	Funatsu[52]	Japan	C/S, CO and nested CC	1612 in C/S 1236 in CO	↓	Subjects with steatosis at baseline determined by bright liver score had slightly lower consumption of coffee (in cross-sectional analysis) and borderline significant after 5 years.
2015	Dickson[53]	US	C/S	1005 subjects without T2DM	↓	Caffeinated coffee (but not decaffeinated) inversely associated with liver fat score (fasting insulin, ALT, AST, metabolic syndrome); not for Fetuni-A. Adjusting for insulin sensitivity attenuated the inverse association suggesting caffeine may increase insulin sensitivity, reduce hepatic fat, and therefore reduce liver enzymes.
2015	Zelber-Sagi[54]	Israel	C/S & CO	347 in C/S 141 in CO	→	Steatosis incidence and prevalence unrelated to coffee consumption adjusting for smoking, sugar consumption and physical activity and identified using liver brightness score as well as SteatoTest (combination of 9 biomarkers and age, gender, weight and height)
2015	Imatoh[55]	Japan	C/S	1024	↓	Lower odds for hepatic steatosis identified by bright liver score when consuming >3 cups coffee/day 0.59 (95% CI: 0.38-0.90) compared with no coffee after adjusting for age, BMI, smoking, alcohol and green tea consumption
2017	Alferink[56]	Holland	C/S within CO	2424	→	No difference in proportion of steatosis between subjects with coffee intake ≥3 cups a day compared to <3 cups a day (34.2% versus 35.2% p=0.656) identified using hyper-echogenic liver ultrasound appearance
2018	Veronese[57]	Italy	C/S	2819	→	Odds of steatosis not significantly different between ≥3 coffee cups a day versus none (OR 0.97 (95% CI 0.71 to 1.32)) identified using ultrasound diagnosed steatosis (semi-quantitative scoring system). Same finding for any,1 cup a day, and 2 cups a day versus none.

C/S: Cross-Sectional; CO: Cohort; CC: Case-control

As previously described, steatosis, or fatty liver, is the most common stage of NAFLD, and most people with steatosis will not progress further along the pathological pathway. It was approximately twenty years after researchers started investigating associations between coffee consumption and liver enzymes that attention turned to coffee consumption and steatosis. This interest mirrored the rising prevalence of type II diabetes, obesity and metabolic syndrome, and their known associations with hepatic steatosis. More advanced stages of NAFLD, such as cirrhosis, had already been the subject of investigation (section 1.6.4).

Existing evidence draws mixed conclusions regarding whether coffee consumption is beneficially associated with the presence of steatosis. Studies have varied in how they have assessed steatosis with some using diagnostic liver fat scoring systems, and others determining the presence of steatosis using ultrasound and bright liver scores. Bright liver score is a technique for evaluating severity of steatosis due to a diffusely enhanced echogenicity caused by fatty infiltration, and a score can range from 0-3[58].

There appears to be no consistent evidence of associations between coffee drinking and lower risk of prevalent steatosis whichever method is used to ascertain the outcome. However, there is heterogeneity in ultrasound diagnostic criteria, ascertainment of coffee consumption, definitions of the coffee comparison groups, and most studies are of cross-sectional in design with relatively small numbers of participants. Misclassification of outcome and exposure could be factors in the lack of significant findings.

A meta-analysis of the studies of Funatsu, Imatoh and Zelber-Sagi, was conducted by Wijarnpreecha et al, and suggested a 29% reduced risk of steatosis for higher coffee consumers (RR 0.71 (95% CI 0.60 to 0.85). However, it may not have been appropriate to have meta-analysed these studies due to heterogeneity of their design including classification of exposure.

1.6.3 Coffee consumption and Non-alcoholic steatohepatitis (NASH) and Fibrosis

A summary of the studies investigating coffee consumption and fibrosis are presented in Table 4.

Table 4: Coffee consumption and liver fibrosis studies

Year	Author	Setting	Study Design	No. of cases/ controls or total subjects	Effect	Main findings
2010	Modi[59]	US	C/S	117	↓	Greater than 2.25 coffee cup equivalent caffeine (coffee) consumption associated with reduced liver fibrosis OR 0.25 (95% CI: 0.09 to 0.67) after adjusting for age, gender, alcohol intake and BMI. No association with non-coffee caffeine and fibrosis. Fibrosis identified from liver biopsy.
2011	Molloy[60]	US	C/S NASH	306	↓	Coffee consumption in NASH stage 1-2 was significantly greater than that in subjects with NASH stages 3-4 and was associated with less fibrosis; coffee consumption was not significantly different between subjects with steatosis and NASH stage 1-2; coffee may protect when other injurious factors present
2012	Anty[61]	France	C/S	195	↓	Regular (filtered) coffee consumption lower in bariatric patients with significant fibrosis; not in espresso drinkers. Authors hypothesised that sugar added to espresso negated any liver benefit. Fibrosis identified from liver biopsy.
2013	Machado[62]	Brazil	C/S	136	↓	Lower advanced fibrosis in subjects with >123 mg/day coffee caffeine in a population of treatment naïve HCV
2014	Bambha[63]	US	C/S	782	↓	Coffee consumers with less IR had significantly lower odds of advanced fibrosis but not in those with higher IR. Authors hypothesised that coffee may only confer benefit below a certain threshold of high oxidative stress caused by conditions such as diabetes, overweight or smoking. A paradoxical benefit was seen with small quantities of alcohol protecting against more severe fibrosis.
2015	Zelber-Sagi[54]	Israel	C/S & Co Fibrosis & NASH	347/147	→	Fibrosis and NASH unrelated to coffee intake using a diagnostic score called the NashTest.
2017	Alferink[56]	Holland	C/S within Co	2424	↓	Lower proportion of LSM≥8Kpa in subjects consuming ≥3 coffee cups a day compared to >0-3 cups and 0 cups (p for trend =0.006).

NASH is characterised by steatosis with inflammation and hepatocyte ballooning, with or without the presence of fibrosis, and represents a progression from simple steatosis[4]. Only two studies have investigated the association of coffee drinking with risk of NASH. One of these screened 306 healthy volunteers for the presence of steatosis using ultrasound[60]. Those with steatosis underwent a liver biopsy and found that coffee consumption in NASH stage 1-2 was significantly greater than that in subjects with NASH stages 3-4 and was associated with less fibrosis; there were no differences in coffee consumption between those with simple steatosis and NASH stage 1-2. The authors hypothesised that coffee may have benefit when other injurious factors were present that could otherwise result in disease progression. The study was strengthened by using liver biopsy to diagnose NASH, but as a result only included a small number of participants. The only other study that focused on NASH used a diagnostic score called the NashTest and found no significant association between coffee drinking and NASH in a fully adjusted model[54].

Several other studies have focused on coffee consumption and risk of liver fibrosis. These studies of mainly cross-sectional design have utilised different methodologies and in different populations. Studies have varied in classification of coffee exposure and measurement of the outcome of fibrosis. Some studies performed liver biopsies and other, more recent studies, used non-invasive techniques such as liver stiffness measurement (described in section 1.5.3.) However, despite these differences, coffee consumption (but not non-coffee caffeine) appears to be consistently associated with lower risk of fibrosis.

Few studies investigated the outcome by coffee type. Anty et al found that there was significantly lower consumption of regular (filtered) coffee in severely obese patients awaiting bariatric surgery with more severe fibrosis, but that the association was not present in those that drank espresso[61]. The authors suggested this could be due to the co-consumption of sugar with espresso with negative hepatic consequences. This finding was supported by a US based study in which higher coffee consumption was only inversely associated with degree of fibrosis in those with low HOMA-IR measured insulin resistance, but not in those with HOMA-IR high insulin resistance[63]. It is possible that coffee consumption confers a benefit in reducing risk of fibrosis but only below a certain threshold of high oxidative stress from conditions such as diabetes (or insulin resistance), overweight or smoking[51,64]. In patients diagnosed as having non-alcohol related liver damage there appeared to be a paradoxical association of lower severity of fibrosis seen in subjects consuming small amounts of alcohol compared to no alcohol[63].

In a meta-analysis by Liu et al, ANY coffee consumption when compared to NO coffee consumption was associated with a 27% lower risk of liver fibrosis (0.73 (95% CI: 0.58 to 0.92))[65]. In a more recent meta-analysis, Shen et al found no significant mean difference in caffeine consumption by degree of fibrosis, but in subgroup analysis there was a significant difference in mean consumption of regular (caffeinated) coffee with lower consumption associated with more severe fibrosis[66].

In summary, in contrast to steatosis, there appears to be more consistent evidence for beneficial associations of coffee consumption (but not non-coffee caffeine) and lower risk of liver fibrosis or fibrosis severity. This suggests that a component of coffee other than caffeine may have an important role in the protective effect. Several of these studies suggest that coffee may mediate a protective effect in fibrosis by interacting with other potential injurious factors such as alcohol and HCV but only below a threshold of high oxidative stress. Caffeine may have a synergistic relationship with other biological compounds in coffee and coffee rather than non-coffee caffeine may be essential. The lack of effect from decaffeinated coffee consumption further backs this as a hypothesis although risk estimates using decaffeinated coffee will often stem from relatively small numbers of participants compared to caffeinated coffee. This is in contrast to the studies investigating coffee consumption and liver enzymes described in section 1.6.1, where non-coffee caffeine also appeared to have some effect.

1.6.4 Coffee consumption and cirrhosis

A summary of the studies investigating coffee consumption and cirrhosis are presented in Table 5.

Table 5: Coffee consumption and liver cirrhosis studies

Year	Author	Setting	Study Design	No. of cases/ controls or total subjects	Effect	Main findings
1992	Klatsky[67]	US	Cohort	68/128934	↓	Coffee drinking inversely related to alcohol but not non-alcoholic cirrhosis hospitalisation; Risk 1/5 in subjects drinking ≥4 cups/day; tea un-associated; small number of events
1994	Corrao[68]	Italy	Case-C	115/167	→	Inverse association between coffee and alcoholic cirrhosis but did not reach significance
2001	Corrao[69]	Italy	Case-C	274/458	↓	Lower cirrhosis risk with increasing coffee consumption OR 0.23, 0.21, 0.16 for 2,3 & 4 cups/day (all statistically significant); no effect from non-coffee caffeine; effects independent of alcohol and viral hepatitis; cases were those admitted with decompensated cirrhosis
2002	Gallus[70]	Italy	Case-C	101/1538	↓	Lower cirrhosis risk with increasing coffee consumption OR 0.57, 0.29 for 2 or ≥3 cups/day; no associated with decaffeinated, tea or cola
2003	Tverdal[71]	Norway	Cohort	53/51306	↓	Liver cirrhosis mortality lower with increasing coffee consumption RR 0.6 (95% CI: 0.5 to 0.80); Includes both alcoholic and non-alcoholic cirrhosis
2006	Klatsky[72]	US	Cohort	330/125580	↓	Coffee drinking associated with lower risk of alcoholic but not non-alcoholic cirrhosis RR 0.6, 0.2 for 1-2 and ≥4 cups/day respectively; cases were those admitted with cirrhosis
2010	Stroffolini[73]	Italy	C/S	137/632	↓	Coffee reduces alcohol related risks of cirrhosis; HBV/HCV increase alcohol related risks
2013	Walton[74]	UK	Case-C	95/220	↓	Patients with cirrhosis drank significantly less coffee than patients with chronic liver disease but without cirrhosis; there was no difference in the amount of coffee consumed by patients with chronic liver disease and a control group of orthopaedic patients
2014	Goh[75]	Singapore	Cohort	114/63275	↓	Inverse association between coffee drinking and non-viral hepatitis related cirrhosis mortality; not with HBV +ve
2017	Setiawan[76]	US	Cohort	2786/215,000	↓	Coffee drinking associated with lower risk of total, cirrhotic and non-cirrhotic NAFLD; total ≥4 cups 0.66 (95% CI 0.53 to 0.83), non-cirrhotic 0.66 (95% CI 0.51 to 0.84), and cirrhotic 0.74 (95% CI 0.44 to 1.23). (p-value for trend significant). Diagnostic classification using ICD-9 codes.

In contrast to the mainly cross-sectional study design of studies investigating associations between coffee consumption and liver enzymes, steatosis, NASH, and fibrosis, studies on cirrhosis have used mainly case-control and cohort designs. These studies have varied in the number of participants, population, and ascertainment of coffee exposure and outcome. Whilst findings have generally shown coffee consumption having a beneficial effect on lower risk of cirrhosis, studies have varied as to how they have approached estimation across aetiologies. For example, Klatsky et al showed that coffee consumption was associated with lower risk of hospitalisation for cirrhosis in alcoholic (identified as those with heavy alcohol consumption) but not non-alcoholic cirrhosis. Others have not tried to determine the aetiology of cirrhosis for each included patient but how exposure to alcohol and hepatic viruses affected the association between coffee and cirrhosis. Only one study made a clear distinction as to cirrhosis caused by NAFLD. This was a nested case control study within a large US cohort that included 2786 cases of NAFLD and 215,000 participants and found that coffee drinking was associated with a 44% lower risk of total and non-cirrhotic NAFLD, and a 26% lower risk of cirrhotic NAFLD comparing ≥4 cups a day with no coffee but the risk estimate for cirrhosis did not reach statistical significance[76]. The cohort was multi-ethnic and risk was consistent across ethnicities. A strength of the study was the validation of the instrument used to capture coffee drinking data, but there was no imaging or biochemical testing of cases and diagnosis was based on ICD-9 codes in Medicare claims.

There appears to be a substantial quantity of evidence suggesting coffee consumption is associated with lower risk of cirrhosis. This fits with the negative associations between coffee consumption and liver fibrosis discussed in section 1.6.3 and together suggest that coffee may reduce the risk of progression of liver disease from fibrosis to cirrhosis. However, all studies were cohort or case-control, and therefore only represent a moderate strength of evidence. There have been two meta-analyses looking specifically at coffee and cirrhosis. Summary estimates suggested that coffee was beneficially associated with risk of cirrhosis. One of the most recent by Kennedy et al suggested a 17% lower risk of cirrhosis for each additional cup of coffee consumed per day compared to none 0.83 (95% CI: 0.78 to 0.88)[77] whilst in an earlier meta-analysis by Liu et al, ANY versus NO coffee consumption was associated with a 39% reduction (0.61 (95%CI: 0.45 to 0.84)) in cirrhosis and HIGH versus LOW (or NO) coffee consumption associated with a 47% reduction (0.53 (95%CI: 0.42 to 0.68)).[65]

1.6.5 Coffee consumption and hepatocellular carcinoma

A summary of the articles investigating coffee consumption and HCC can be seen in Table 6.

Table 6: Coffee consumption and liver cancer

Year	Author	Setting	Study Design	No. of cases/ controls or total subjects	Effect	Main findings
2002	Gallus[78]	Italy & Greece	Case-C	834/1912	↓	Coffee inversely associated with HCC but fully adjusted CI touched unity
2005	Inoue[79]	Japan	Cohort	334/90472	↓	Drinking coffee associated with lower risk of HCC in men and women combined; not for green tea
2005	Shimazu[80]	Japan	Cohort	117/78950	↓	≥1 cup/day coffee RR 0.58 (95%CI: 0.36-0.96) in risk of HCC
2005	Gelatti[81]	Italy	Case-C	250/500	↓	In decade before diagnosis, coffee drinking inversely associated with HCC; benefits persisted across aetiologies
2005	Kurozawa[82]	Japan	Cohort	258/110688	↓	HCC risk lower in subjects drinking ≥1 cup coffee/day HR 0.50 (95% CI 0.31-0.79); significant in men but not in women
2007	Montella[83]	Italy	Case-C	185/412	→	Inverse association between coffee and HCC but did not reach significance and no relation in decaffeinated coffee or tea
2007	Tanaka[84]	Japan	Case-C	209/1964	↓	Recent and 10 years before coffee drinking inversely associated with risk of HCC
2007	Wakai[85]	Japan	Nest CC	96/3444	↓	Coffee drinkers versus non-drinkers lower risk of HCC including total, HCV +ve and –ve subjects
2008	Hu[86]	Finland	Cohort	128/60323	↓	Highest risk of HCC in those with low coffee consumption and high GGT
2009	Inoue[87]	Japan	Cohort	362/63257	↓	Increased coffee consumption associated with reduced risk of liver cancer and with either or both HBV or HCV. Not in green tea.
2011	Johnson[88]	Singapore	Cohort	362/63257	↓	High coffee or caffeine consumption associated with reduced risk of HCC HR 0.56 (95% CI: 0.310-1.00) p=0.049 for ≥3 cups/day
2013	Lai[89]	Finland	Cohort	213/27037	↓	Both filtered and boiled coffee associated with lower risk of HCC RR 0.82 (0.72 to 0.93) per cup/day (p=0.0007 for trend)
2013	Jang[90]	Korea	Case-C	258/1106	↓	Lifetime coffee consumption independent factor that reduces risk of HCC but not in HBV +ve subjects
2014	Bamia[91]	Europe	Cohort	201/486799	↓	Increased coffee and tea associated with lower HCC risk; not decaffeinated
2015	Setiawan[92]	US	Cohort	451/162022	↓	High coffee consumption associated with reduced risk of HCC; RR 0.62, 0.59 for 2-3 & ≥4 cups/day respectively
2015	Petrick[64]	US	Cohort	860/1212893	↓	Higher coffee associated with lower risk of HCC RR 0.73 (95% CI: 0.53-0.99) for >3 cups/day; Not for intrahepatic cholangiocarcinoma
2015	Aleksandrova[93]	Europe	Nest CC	125/250	↓	Reduced risk of HCC with coffee drinking partly explained by biomarkers of inflammation and hepatocellular injury
2018	Wiltberger	Europe	Cohort	16/90	↓	Lower risk of recurrence of HCC following liver transplant in ≥3 cups coffee/day compared to <3 cups/day – HR 0.29 (95% CI 0.12 to 0.71)

2018	Park	US	Cohort	167,720	↓	Lower risk of HCC 2-3 cups/day vs none HR 0.66 (0.48 to 0.85); ≥4 cups/day vs none HR 0.57 (0.38 to 0.87)
2019	Tran	Europe	Cohort	88/471,779	↓	Lower risk of HCC in any coffee drinker versus none, HR 0.50 (95% CI 0.29 to 0.87) and findings consistent between instant and ground coffee

There appears to be an inverse association between coffee consumption and hepatocellular carcinoma (HCC). This appears consistent across a range of study designs, populations, coffee drinking cultures (with different popularity amongst preparation types) and aetiologies, and extends to both diagnosis and mortality.

Most studies were of cohort design with less risk of bias from reverse causality compared to case-control studies where participants may alter their coffee consumption in response to symptoms or knowledge of a diagnosis. Several studies performed additional analyses excluding diagnoses within early years of exposure ascertainment and found similar negative associations[80,82]. However, it is not clear the typical interval between cellular pathology and clinical manifestation and some degree of reverse causality may be inherent. Cohort studies also tend to only include a small number of cases of HCC but this is often offset by the benefits of the prospective designs in eliminating recall bias and reverse causality if years of follow up have been sufficient.

Most studies have adjusted for other potential confounders including alcohol, smoking and infective hepatitis. Infective hepatitis is a risk factor for HCC and the beneficial association of coffee consumption and HCC appears to be consistent irrespective of aetiology. The presence of unmeasured viral hepatitis status may confound the association between coffee drinking and HCC so importantly many studies have measured and adjusted or stratified their analysis to account for this. In a nested case-control study of Japanese patients, coffee consumption was negatively associated with HCC in total and both hepatitis C positive and negative subgroups[85]. This was also the case in a Japanese cohort study including 362 cases and 63257 subjects[87]. The risk reduction extended to subjects with and without both hepatitis B and C infection. However, in a Korean case-control study lifetime coffee exposure was associated with overall lower risk of HCC but not in subjects with Hepatitis B infection[90]. Despite both causing chronic hepatic injury and fibrosis the pathological pathway to HCC is different. For hepatitis C, the virus increases oxidative stress and steatosis in hepatocytes, whereas hepatitis B can pathologically transform hepatocytes directly by integration into the host genome[90]. Coffee consumption appears to lead to a stabilisation of chromosomal DNA and therefore reduces risk of neoplastic change. In a crossover randomised controlled trial of 40 patients with hepatitis C exposed to 4 cups coffee per day, Cardin et al, found a reduction of oxidative damage was seen in 88% of the sample and 89% showed increase in telomere length corresponding to greater DNA stability[94]. There was also a reduction in pro-collagen III as a serum marker for fibrosis in 70% of the patients.

There have been a series of meta-analyses investigating coffee and HCC risk published since 2007, with four published by different groups in 2016-17. There appears to be consensus that high coffee consumption compared with low or no coffee consumption is associated with approximately 50% lower HCC risk, and 15-20% reduction for each extra cup of coffee consumed each day. There does not appear to be a beneficial association with decaffeinated coffee or tea consumption. In conclusion, there does appear to be a substantial body of evidence that coffee consumption is inversely associated with HCC, but similar to other liver outcomes, the observational nature of studies means they represent only moderate strength of evidence.

1.6.6 Coffee consumption and liver outcome meta-analyses

A summary of coffee consumption and liver health systematic reviews and meta-analyses can be seen in Table 7.

Table 7: Coffee consumption and liver disease Systematic Reviews and Meta-analyses

Year	Author	Condition	No. of studies	No. of cases	Effect	ANY versus NONE	HIGH versus LOW	Extra 1 cup/day
2007	Bravi[95]	HCC	10	2260	↓	0.59 (95%CI: 0.49 to 0.72)	0.45 (95%CI: 0.38 to 0.53)	0.77 (95%CI: 0.72-0.82)
2007	Larsson[96]	HCC	9	2260	↓	np	np	0.75 (95% CI: 0.70 to 0.82)
2013	Bravi[97]	HCC	16	3153	↓	0.60 (95%CI:0.50 to 0.71)	0.44 (95% CI: 0.39 to 0.50)	0.80 (95% CI: 0.77 to 0.84)
2013	Sang[98]	HCC	16	3622	↓	np	0.50 (95%CI: 0.42 to 0.59)	np
2015	Liu[65]	Fibrosis	16	3034	↓	0.73 (95% CI: 0.58 to 0.92)	np	np
2015	Liu[65]	Cirrhosis	16	3034	↓	0.61 (95%CI: 0.45 to 0.84)	0.53 (95%CI: 0.42 to 0.68)	
2015	Jaruvongvanich[99]	HCV Fibrosis	5	1507 participants	↓	np	0.39 (95%CI: 0.21 to 0.72)	np
2016	Bravi[100]	HCC	12 (cohort)	3414	↓	0.66 (95%CI: 0.55 to 0.78)	0.50 (95%CI: 0.43 to 0.58)	0.85 (95%CI: 0.81 to 0.90)
2016	Bai[101]	HCC	11	2795	↓	0.49 (95%CI: 0.46 to 0.52)	0.21 (95%CI: 0.18 to 0.25)	np
2016	Yu[102]	HCC	10 (cohort)	3389	↓	np	0.55 (95%CI: 0.44 to 0.67)	np
2016	Kennedy[77]	Cirrhosis	9	1990	↓	np	np	0.83 (95% CI: 0.78 to 0.88)
2016	Shen[66]	NAFLD	6	2299	↓	Regular coffee but not total caffeine significantly associated with reduced risk of hepatic fibrosis of NAFLD		
2017	Kennedy[103]	HCC	17	4730	↓	np	np	0.81 (95% CI: 0.77 to 0.85)
2017	Godos[104]	Biliary Tract Cancer	5	726	↓	np	0.83 (95% CI: 0.64 to 1.08)	np
2017	Godos[104]	Liver cancer	13	4227	↓	np	0.52 (95% 0.42 to 0.63)	np but linear dose-response evident
2017	Wijarnpreecha[105]	Steatosis	3	2407 participants	↓	0.71 (95% CI: 0.60 to 0.85)	np	np
2017	Wijarnpreecha[105]	Fibrosis	3	883 participants	↓	0.70 (95% CI: 0.60 to 0.82)	np	np
2018	Chen[106]	NAFLD	7	4825	↓	Np	np	0.94 (95% CI: 0.92 to 0.97)

np: not published

1.7 Biological plausibility of coffee associations with liver health

1.7.1 Pathophysiology of NAFLD

The majority of people with the initial stage of NAFLD, steatosis, do not progress along the pathological pathway[107]. Hypotheses for mechanisms that trigger progression have traditionally focused on a two-hit process[108]. The first hit is due to dysfunctional adipose tissue and increasing insulin resistance, leading to increased vulnerability to a second hit. Second hits lead to increased oxidative stress and inflammation, fibrogenesis, and possible further progression to carcinogenesis. More recent hypotheses focus on a multi-hit model where a number of different factors can contribute to the risk of progression including oxidative stress, genetic polymorphisms and inflammatory pathway activation[108]. Even more recently, a distinct-hit model has been proposed in which pure steatosis and NASH are seen as two independent conditions caused by insulin resistance[108]. The pathological pathway is shown in Figure 7 and each stage will be discussed below.

1.7.1.1 Lipid accumulation

The liver has a key role in lipid homeostasis with intrahepatic lipid a balance between acquisition and disposal[109]. Acquisition occurs through uptake of circulating fatty acids and de novo lipogenesis. Disposal occurs through mitochondrial, peroxisome and cytochrome lipid oxidation mechanisms, and through export as very low-density lipoproteins (VLDL). In NAFLD excessive accumulation of liver lipids occurs when acquisition exceeds disposal. The process begins when excessive dietary fat (and carbohydrate) leads to peripheral adipose tissue enlargement[108]. With enlargement, the adipose tissue starts to dysfunction and cell signalling proteins called adipokines are released. These make the adipose tissue resistant to the presence of insulin and in an effort to maintain glucose homeostasis, even more insulin is produced by the pancreas. Without the moderating effect of insulin, adipose tissue begins to release fatty acids into the circulation. The increased circulating fatty acids create ectopic adipose tissue in other tissues such as skeletal muscle. This has the effect of more generalised insulin resistance, including hepatic insulin resistance, worsened by the long distance effects of the adipokines. In this state the liver becomes swamped with the higher levels of circulating insulin, glucose and fatty acids, because the

usual physiological mechanism of insulin driving glucose into cells is simply not working.

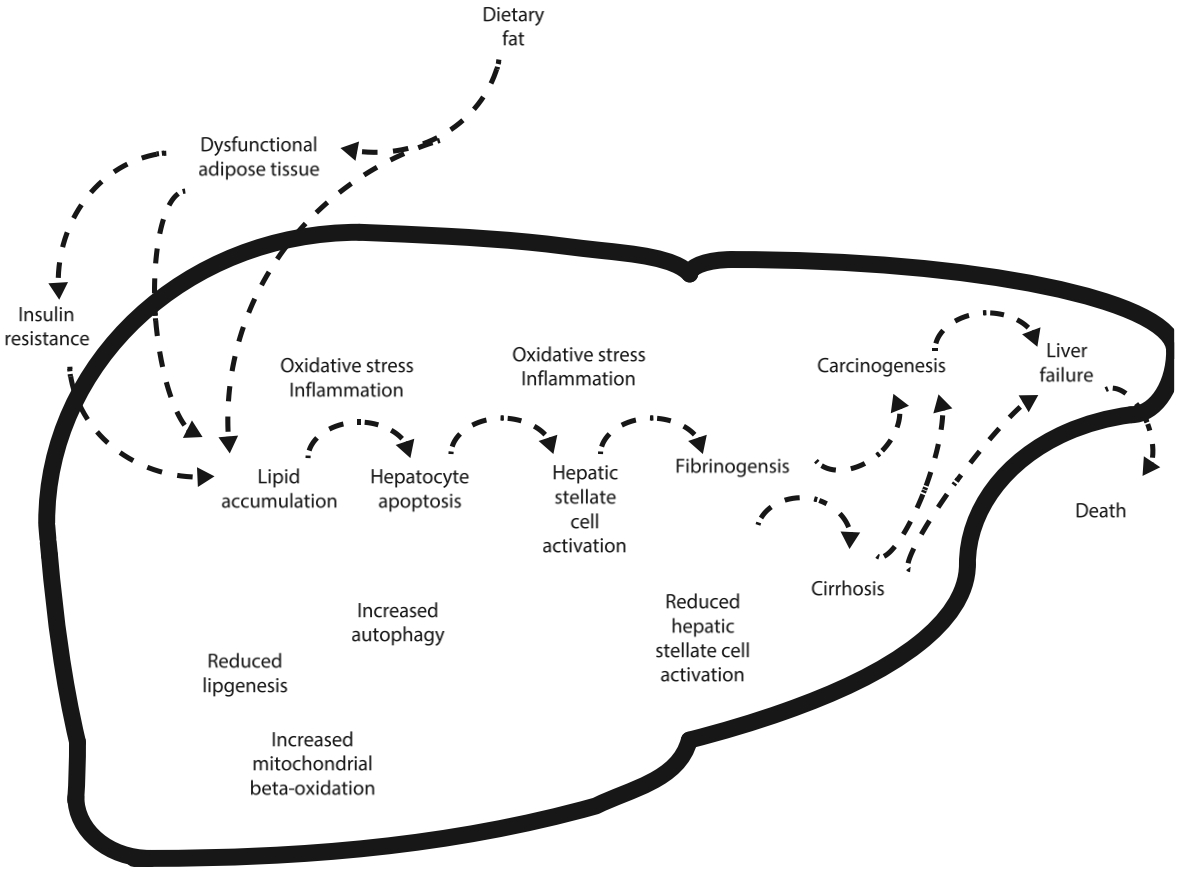


Figure 7: Pathological pathway of NAFLD

Circulating lipids are taken into hepatocytes via plasma membrane transporters regulated by peroxisome proliferator-activated receptor γ (PPARγ)[109]. Rather than reduce its own lipid synthesis in compensation, the liver actually worsens lipid accumulation by de novo lipogenesis from carbohydrate derived Acetyl-CoA. This is driven by transcription factors sterol regulatory element binding protein 1c (SREBP-1c) and carbohydrate regulatory element binding protein (ChREBP) in response to FFA and glucose respectively[108]. Further lipid accumulation occurs due to impaired formation of VLDL, impaired LDL endocytosis, and impaired usage from mitochondrial β-oxidation. Peroxisome proliferator-activated receptor α (PPARα) controls energy production from fatty acid oxidation. When β-oxidation in mitochondria is overwhelmed, more oxidation shifts to peroxisomes and cytochromes, generating more reactive oxygen species[109]. Hepatic insulin resistance exacerbates new glucose synthesis (gluconeogenesis) and breakdown of glycogen (glycogenolysis) via the downregulation of Phosphoenolpyruvate carbinase and Glucose-6-phosphatase. The resulting accumulation of lipids in the liver can trigger oxidation, inflammation, apoptosis and fibrosis that are characteristic of NASH[108].

1.7.1.2 Oxidative stress, inflammation and hepatocyte apoptosis

Excess accumulation of lipids in the liver leads to oxidative damage of lipids, protein, and DNA, which in turn triggers inflammation and fibrogenic signalling[108]. Increased mitochondrial β-oxidation due to excess free fatty acids is a pro-oxidising factor that damage the same mitochondria that have produced them. The activity of the cytochrome P450 enzyme, CYP2E1, usually inhibited by insulin, is increased leading to further oxidation and NASH progression. NADPH oxidase 4 (NOX4) is also implicated by generating superoxide and hydrogen peroxide from molecular oxygen leading to endoplasmic reticulum stress and increased apoptosis in hepatocytes. Oxidation is also associated with iron overload. In simple steatosis the anti-oxidant activity is enhanced through the over expression of superoxide dismutase and catalase enzymes, but in NASH such anti-oxidant compensation is overwhelmed by the pro-oxidative state with suppression of these enzymes and over-consumption of anti-oxidant molecules such as glutathione and co-enzyme 10.

Inflammation in NASH results from intra and extrahepatic inflammatory factors[108]. Intrahepatic factors are released from hepatocytes and Kupffer cells. Extrahepatic factors are released from adipose tissue and intestine. Dysfunctional adipose tissue releases pro-inflammatory cytokines TNF-α, IL-1 β, IL-6, IL-8 and MCP-1. Macrophages in adipose tissue worsen the situation by switching to a pro-inflammatory phenotype and contributing to the release of cytokines. The hormone leptin is also released from the adipose tissue that further activates macrophages via the JAK/STAT signalling pathway, whilst beneficial adiponectin is reduced. Endotoxin lipopolysaccharides arriving in the portal circulation from the intestine are also implicated. These are fragments of bacterium from the microbiome that pass through the intestinal wall and in the liver they activate toll-like receptor 4 (TLR4) in hepatocytes, Kupffer cells and hepatic stellate cells, and this leads to MAPKs and NF-κB and AP-1 releasing cytokines TGF-β and IL-8. The effect of this is to attract neutrophils with oxidative stress causing hepatocyte injury.

Hepatocellular death in NASH, caused by accumulation of damaged cellular products due to dysfunctional autophagic function, distinguishes it from steatosis, and the extent of this correlates with the degree of liver injury[108]. Compensatory progenitor cell expansion is triggered as a result and this predisposes to cirrhosis and HCC.

1.7.1.3 Hepatic stellate cell activation and fibrogenesis

Hepatocyte apoptosis triggers hepatic stellate cell activation[108]. HSCs are usually in a quiescent state, but in response to hepatocyte apoptosis they transform into myofibroblasts and lay down an extracellular matrix, and this is subsequently replaced with collagen in order to ensure tissue integrity. This process is regulated by both the Kupffer cells, which secrete TGF-β, and the hepatocytes. TGF-β promotes hepatic stellate proliferation and enduring myofibroblast phenotype via the TGF-β/SMAD3 pathway. NOX4 also leads to activation of hepatic stellate cells and fibrogenesis. Connective tissue growth factor (CTGF) is another downstream pro-fibrotic mediator and is also activated directly by glucose and insulin. As fibrosis advances towards cirrhosis, leptin increases, adiponectin reduces, and the liver loses fat[110].

The hedgehog signalling pathway, responsible for embryonic cell differentiation, is also implemented in progression along the NAFLD pathway[108]. Liver injury in NASH leads to the wound healing after hepatocyte loss and hedgehog ligand expression, which leads to promotion of the resident liver stem cells aimed at repairing the damaged liver tissue. Overstimulation of the pathway halts the process at the fibrogenesis stage rather than completely repairing the liver tissue. The increased proliferation of progenitor cells is a situation that can predispose to carcinogenesis.

1.7.2 Biological plausibility of coffee in hepatoprotection

The epidemiological observations of coffee drinking and associations with lower risk of fibrosis, cirrhosis, and HCC have preceded understanding of molecular mechanisms behind coffee benefit. However, numerous in vitro and in vivo studies have began to unveil mechanisms in which coffee, or compounds within coffee, can exert a beneficial influence on some of the molecular pathways described in the previous section. Two recent reviews have summarised current molecular understanding of coffee and hepatoprotection.[111,112] Figure 8 shows pathways in which existing studies have demonstrated an influence of coffee in reducing the progression of NAFLD.

Much as progression along the NAFLD pathway may be a result of multiple unfavourable biochemical ‘hits’, coffee, and coffee compounds, appear to be able to hit back at multiple molecular pathways associated with NAFLD. Coffee appears to reduce lipid accumulation, reduces oxidative stress and inflammation, reduces hepatic stellate cell activation and hence fibrogenesis, and reduce carcinogenesis[111,112]. A summary of the beneficial effects

of whole coffee, decaffeinated coffee, caffeine, chlorogenic acids, diterpenes and melanoidins, as evidenced from various studies, are presented in Table 8.

Coffee exerts an influence in reducing de novo lipogenesis through the down regulation of SREB1c[111]. Additionally usage of FFA is enhanced through increased mitochondrial β-oxidation driven by increased PPARα. Finally intracellular lipid is diminished through enhanced autophagy via an increase in the energy sensor AMP-activated protein kinase[112]. Progression towards fibrosis is reduced through anti-oxidant effects of increased glutathione (an established antioxidant[113]) and Nrf2[114], and anti-inflammatory effects of reduced TNFα, IL-6 and IL-1β. Antagonism of the adrenergic A2A receptor leads to a reduction in HSC activation, defective adhesion and increased apoptosis. This occurs via down-modulation of TGF-β induced CTCF expression via SMAD2 degradation in hepatocytes and by reducing tissue inhibitor of metalloproteinase 1, α-SMA and procollagen type 1c in HSCs[115]. Finally, coffee appears to reduce the risk of progression towards carcinogenesis through an increase in phase II carcinogen detoxifying enzymes[116], blocking phase I activating enzyme[116], increasing matrix metalloproteinases 2 to tissue inhibitors of MMP ratio (MMP2/TIMP) and increasing the enzyme glutathione S-transferase (GST)[112].

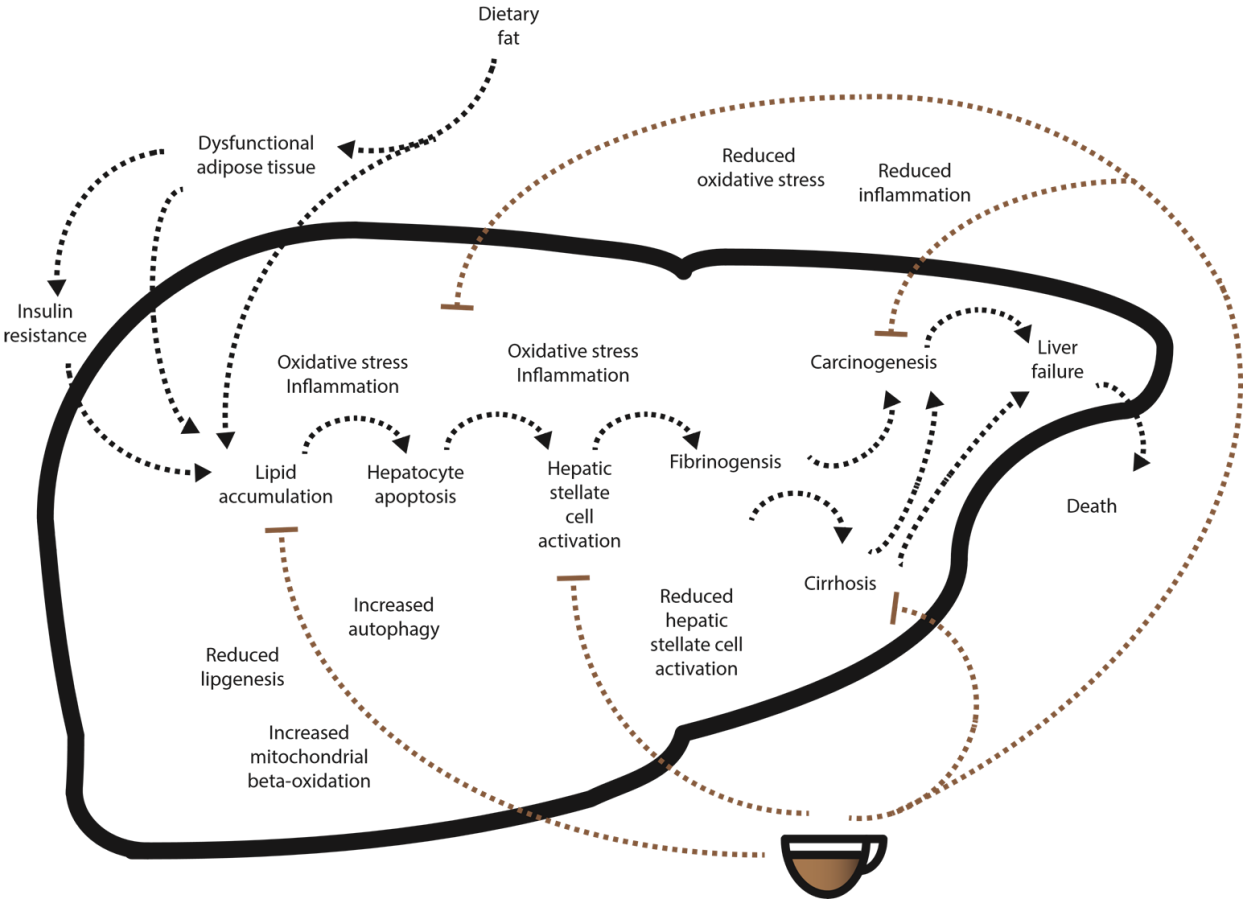


Figure 8: Coffee interacting with the pathological pathway of NAFLD

Table 8: Summary of the beneficial effects of coffee

Coffee/coffee compound	Antisteatogenic		Antifibrotic			Anticarcinogenic
	↓liopgenesis	↓ Lipid accumulation	↓ Oxidative stress	↓ Inflammation	↓ fibrogenesis	↓ carcinogensis
Whole coffee		↓ PPARγ	↑ Glutathione	↓ pro-inflammatory cytokines	↓ TGF-β ↓ collagen content ↓ MMP2	↑ Nrf2 ↑ phase II carcinogen-detoxifying enzymes
Decaffeinated coffee		↑ PPAR-α ↑ autophagy ↓bacterial endotoxin in portal blood	↓oxidative stress	↑ anti-inflammatory cytokines ↓pro-inflammatory cytokines	↓collagen ↓TGF-β	
Caffeine	↓SREB1c	↑ β oxidation	↑ Nrf2 ↑ Glutathione	↓pro-inflammatory cytokines	↓TGF-β ↓CTGF ↓collagen content ↑SOD ↓Adenosine A2A receptor	↑ GST
Chlorogenic acid	↓SREB1c	↑ AMPK ↓PPARγ ↑ β oxidation	↓ROS formation ↑ Nrf2	↑ anti-inflammatory cytokines ↓pro-inflammatory cytokines	↓collagen content	↓MMP2/TIMP ratio
Diterpenes			↑ Glutathione	↓pro-inflammatory cytokines	↓TGF-β ↓ CYP2E1	↑ GST ↓Carcinogen-activating enzymes
Melanoidins			↓oxidative stress		↓TGF-β	

1.8 Summary

Twenty-five years of observational research has been largely consistent in finding beneficial associations between coffee drinking and more advanced stages of NAFLD. There appears to be consistency in the association in different populations, different study designs, and different aetiologies for a variety of different liver-related outcomes. Common pathological pathways between outcomes possibly help to explain these consistent associations. Less clear is whether the beneficial associations of drinking coffee are independent or whether coffee interacts with other risk factors such as alcohol to lessen risk factor-related liver damage. Also unclear is which of the 1000 bioactive compounds in coffee may be responsible for the beneficial effects. Decaffeinated coffee consumption has generally not been associated with liver outcomes. This may be due to the smaller number of study subjects who drink decaffeinated coffee and thus the associations are underpowered to show an effect or that the beneficial associations of coffee truly require caffeine. Decaffeinated coffee drinkers may also be different from caffeinated coffee drinkers in ways other than coffee consumption[117]. For example, they may be more healthful and choose to drink decaffeinated coffee if they believe that caffeine has negative health consequences. They may also be more likely to suffer with other health conditions or take medications that have impacted on their preference for decaffeinated coffee. There is no consistent association between liver health outcomes and the consumption of caffeine from other sources such as tea and cola. Caffeine from other sources may not have reached a threshold level for benefit since they contain much less caffeine per drink compared with caffeinated coffee. Alternatively, coffee caffeine may work in synergy with other bioactive compounds in coffee such as the polyphenols, known to have considerable anti-oxidant potential, in order to exert beneficial effects. When competing oxidative stress exceeds a certain threshold, coffee consumption alone may not be powerful enough to provide sufficient antioxidant activity, as might be the case in subjects with significant obesity, type II diabetes or who smoke.

1.8.1 Rationale for planned programme of work

Nearly every observational study investigating the association between coffee consumption and liver outcomes have acknowledged the limitations of observational research that can suggest associations and not infer causation. The key reason for this is due to the presence of residual confounding from known or unknown variables. Therefore,

they have invariably suggested the need for further research, and specifically interventional studies where randomisation between intervention and control distributes confounders equally between groups. This serves to strengthen evidence for causation between an exposure and an outcome. However, there are inherent complexities in conducting such trials, which is why there have been no randomised controlled trials to date to investigate whether drinking more coffee can reduce progression of NAFLD. Due to the huge prevalence of NAFLD, linked to the rise in obesity and type II diabetes, understanding whether drinking more coffee could reduce the risk of progression of steatosis to fibrosis, or fibrosis to cirrhosis would be an extremely important addition to the research knowledge in this area.

Three important considerations must be made before coffee is given as an intervention and the work within this Doctorate of Medicine aims to address these important knowledge gaps. Firstly, whilst coffee appears to be beneficially associated with liver health, it would be important to recognise any harmful associations of coffee consumption with other health outcomes. To address this knowledge gap, an umbrella review of coffee consumption in relation to all other health outcomes was conducted and is presented in Chapter 2:.

Secondly, to address the issue of misclassification of exposure in relation to coffee consumption, a coffee unit measure across different preparation methods was developed using published estimates of coffee constituents. Coffee intake data from a representative UK population was then used to assess the proportion of misclassification likely when cup volume and coffee preparation type was not taken into account. This coffee unit measure could be used to improve ascertainment of coffee consumption in people with NAFLD and could be used in a future randomised controlled trial for baseline and monitoring of consumption and to help classify the intervention. The coffee unit measure development and ascertainment of misclassification is detailed in chapter 3.

Thirdly, it is not known what an intervention to increase coffee consumption in a treatment group should look like. For example, the intervention could be the coffee itself, given as a pre-measured dose, to be taken in addition to the person's usual intake. Alternatively, a participant could drink more of their usual coffee, with the intervention being a way to encourage this change in behaviour such as text message reminders. To address this knowledge gap, and additionally to understand current patterns of coffee drinking in

patients with NAFLD, a mixed-methods study was conducted. This included a qualitative phase, involving 17 semi-structured interviews, and informed the final design of a survey instrument for use in a subsequent quantitative phase in a larger representative population of patients with NAFLD. The objectives of the mixed-methods study were:

- To investigate the pattern of coffee drinking (caffeinated and decaffeinated) including preparation type, frequency, volume, and location
- To investigate the pattern of non-coffee caffeine drinking including type of beverage, frequency, volume and location
- To investigate the pattern of additional ingredients consumed with coffee such as milk and sugar
- To explore whether coffee consumption has changed in people due to their liver condition
- To explore perceptions of barriers and enablers to increasing coffee consumption to inform intervention design
- To explore perceptions regarding the acceptability to patients of a randomised trial based intervention to drink more coffee

Further details of the mixed method study and the qualitative phase results can be found in Chapter 1:, with the quantitative phase presented in Chapter 5:.

1.9 Summary of thesis components

In summary, the

components of the thesis are:

Chapter 2:

A systematically conducted umbrella review to assess the totality of high level evidence of associations of coffee consumption and multiple health outcomes.

Chapter 3:

The development of a coffee unit measure and an assessment of proportion of misclassification of coffee intake in a representative sample of the UK population when coffee cup size and preparation method is not taken into account

Chapter 1:

An exploration of coffee consumption in people with NAFLD and understanding barriers and enablers to increasing their intake using qualitative methods

Chapter 5:

An exploration of coffee consumption in people with NAFLD and understanding barriers and enablers to increasing their intake using quantitative methods

Chapter 6:

Summary of findings and discussion

Chapter 2: Coffee consumption and health: An umbrella review of meta-analyses of multiple health outcomes

2.1 Background

Prior to an interventional approach to evaluate whether coffee can be used as a treatment to reduce the risk of progression in NAFLD it is important to systematically assess the totality of higher-level evidence on associations of coffee consumption with all health outcomes. This approach can help contextualise the magnitude of the association of coffee across health outcomes and importantly assess the existing research for any harm that may be associated with increased consumption. Should there be evidence of additional risks, this would have to be carefully balanced with any benefit in reducing the risk of progression of NAFLD. It would be especially important to understand evidence for associations between coffee consumption and cardiovascular health because as discussed in section 1.1, this is the leading cause of mortality in patients with NAFLD. Therefore, to assimilate the vast amount of research available on coffee consumption and health outcomes, an umbrella review of existing meta-analyses was conducted.

2.2 Methods

2.2.1 Umbrella review methodology

The aim of an umbrella review is to systematically search, organise and evaluate existing evidence from multiple systematic reviews and/or meta-analyses on all health outcomes associated with a particular exposure[118]. The umbrella review methodology was used to conduct a review of coffee consumption and multiple health outcomes. Meta-analyses in which coffee consumption was all or part of the exposure of interest or where coffee consumption had been part of a subgroup analysis, were systematically identified from existing literature. Most published studies measure coffee consumption in cups a day, which lends itself to combining estimates of effect using meta-analysis. Therefore, only meta-analyses were included in the umbrella review, and systematic reviews without meta-analysis were excluded.

2.2.2 Literature Search

Meta-analyses of observational or interventional studies that investigated the association between coffee consumption and any health outcome were identified by an electronic search of PubMed, Embase, CINAHL and the Cochrane Database of Systematic Reviews from inception to July 2017. The following search strategy was used: (coffee OR caffeine) AND (systematic review OR meta-analysis). Truncated terms were used for all fields, and following the SIGN guidance recommended search terms for systematic reviews and meta-analyses[119]. Independently, two researchers (RP and OK) screened the titles and abstracts, selected articles for full text review, and reviewed full text articles for eligibility. Arbitration of any differences that could not be resolved by consensus was provided by a third researcher, PR. A manual search of the references of eligible articles was also performed.

2.2.3 Eligibility criteria and data extraction

Meta-analyses of observational (cohort, case-control and cross-sectional with binary outcomes) and interventional studies (randomised controlled trials) were included in the umbrella review. Meta-analyses that had pooled any combination of relative risks (RR), odds ratios (OR), relative rates or hazard ratios (HR) from studies comparing the same exposure to the same health outcome were included. Articles were included where the coffee exposure was in any human adult population of any ethnicity or gender, healthy or with pre-existing illness, and in all countries and all settings. Articles were included when the exposure was classified as total, caffeinated or decaffeinated coffee. Articles were not included where it was not possible to extract coffee caffeine exposure separately from caffeine exposure. This was because coffee contains numerous biologically active ingredients in addition to caffeine that may interact to produce unique health effects. With the exception of studies of genetic polymorphisms for coffee metabolism, all health outcomes where coffee consumption had been investigated as the exposure of interest were included. Any study investigating HIGH coffee versus LOW coffee exposure, ANY coffee versus NONE, and any linear or non-linear dose-responses, were included. If an article presented separate meta-analyses for several health outcomes, then each of these were included separately.

Data was extracted independently by RP and OK from eligible articles. The first author, journal, year of publication, outcome(s) of interest, populations, number of studies, study design(s), coffee consumption measure(s), coffee consumption measurement capture

method(s), coffee consumption type(s), sources of funding, study-specific exposure categories as defined by authors, risk estimates, the corresponding confidence intervals, number of cases and controls (case-control studies), events, persons/person years and length of follow up (cohort studies), or numbers in intervention and control groups (randomised controlled trials), type of risk used for pooling (RR, OR, HR), and type of effect model used in the meta-analysis (fixed or random), any publication bias estimate, between study variance (tau-squared) and estimates of the proportion of variance reflecting true differences in effect size (I^2), were all extracted for each eligible article. Finally, where a p-value for non-linearity was published in meta-analyses with dose-response relationships, this was also extracted. Any difference in extracted data between the two researchers was resolved by consensus.

2.2.4 Assessment of methodological quality of included studies and quality of evidence

Methodological quality of meta-analyses was assessed using the AMSTAR[120] measurement tool for systematic reviews, which includes ratings for quality in the search, analysis and transparency of a meta-analysis. AMSTAR has been shown to be a reliable and valid tool for both interventional and observational research methodological quality assessment[120,121]. Studies that used a fixed rather than a random effects model for producing a summary estimate were downgraded because we considered the random effects model the most appropriate because we would not expect a single true effect size common to all studies due to the heterogeneity in study designs, populations, coffee preparation methods and cup sizes.

Quality evidence for each outcome was assessed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) working group classification[122] which categorises evidence from systematic reviews and meta-analyses into ‘high’, ‘moderate’, ‘low’ or ‘very low’ quality. Baseline quality of the evidence is dictated by the overall study design but factors such as unexplained heterogeneity or high probability of publication bias would downgrade the quality of the evidence, and a large magnitude of effect or dose-response gradient would increase it.

2.2.5 Method of analysis

Where sufficient exposure and outcome data were available in each article, we re-analysed the meta-analysis using the DerSimonian and Laird random-effects model, that takes into account between-study and within-study variance[123]. Where insufficient data was published we did not review the primary study articles. The summary estimates were computed using the log scale to maintain symmetry in the analysis, and took the exponential to return the result to the original metric. The tau-squared statistic was produced as an estimate of true variation in the summary estimate and the I^2 statistic as an estimate of proportion of variance reflecting true differences in effect size. Egger's regression test[124] was estimated as a measure of publication bias for any re-analyses that included at least ten studies and a p-value <0.1 was considered significant for Egger's test. There was a scarcity of published estimates for number of cases and controls/subjects and estimates for each dose of coffee exposure, needed for a dose-response analysis, and therefore we did not re-analyse any of the dose-response meta-analyses. A test of interaction using the method published by Altman and Bland[125] was used where we were interested in the apparent effect modification by gender.

Forest plots were constructed from the extracted and/or re-analysed data. Three categories of exposure for any health outcome were included where there was data - HIGH coffee versus LOW coffee (or NONE), ANY coffee (regular) versus NONE, and ONE EXTRA CUP/DAY (relative to NONE). Each article presented a meta-analysis using one or more of these exposure categories or calculated combined estimates for a range of cups/day exposures where a non-linear dose-response had been identified. A single health outcome per exposure category was included in each forest plot prioritised as the most recent study available. Where two or more studies were published within the same 24-month period for the same category of exposure and same outcome, the meta-analysis which included the highest number of cohort studies was selected, and where these were identical, the article with the highest AMSTAR score was selected. Where a meta-analysis included both cohort and case-control studies, only data from a cohort study sub-analysis was selected if available, or re-analysed where this was possible. Cohort studies represent a higher form of evidence as less likely to be biased by reverse causality, recall, and selection bias, compared to case-control studies. Linear dose-response analyses presented as two or three extra cups/day were converted to one extra cup/day by taking the square or cube root respectively[126]. Outcomes were colour coded by body system or function to assist in visual representation of the data. Where we were unable to re-analyse

data from a meta-analysis we included summary data as extracted from the meta-analysis article and whichever measure of heterogeneity or publication bias, if any, was available.

2.2.6 Patient Involvement

Feedback from a Patient and Public Involvement (PPI) focus group and from an independent survey of patients with chronic liver disease in secondary care were used to inform the design of the umbrella review. This preliminary work demonstrated enthusiasm from patients in finding out more information about the wider benefits and potential harms of increasing coffee intake, as well as interest in participating in a randomised controlled trial involving coffee as an intervention. The results of this umbrella review were also disseminated during a recent PPI session that had been arranged to gather opinions regarding the acceptability of qualitative research to investigate patterns of coffee drinking in people with Non-Alcoholic Fatty Liver Disease.

2.2.7 Involvement of author

I conceptualised the study, conducted the search for research articles, screened the titles and abstracts and full papers for inclusion, extracted the data from selected research articles, assessed the quality of included studies and the strength of the evidence and was lead author on the published research paper. My colleague OK independently co-screened the titles and abstracts and full papers for inclusion, independently co-extracted the data, independently co-assessed the quality of included studies and the strength of the evidence and performed the meta-analyses and associated heterogeneity and publication bias computation.

2.3 Results

Figure 9 shows the results of the systematic search and selection of eligible studies. The search yielded 201 meta-analyses of observational research, in 135 articles, with 67 unique outcomes, and 17 meta-analyses of randomised-controlled trials, in 6 articles, with 9 unique outcomes. The median number of meta-analyses per outcome for observational research was 2 (interquartile range 1 to 4, range 1 to 11). Twenty-two outcomes had only a single meta-analysis. For meta-analyses of randomised controlled trials, outcomes were

limited to systolic and diastolic blood pressure, total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglyceride, and three pregnancy-related outcomes of preterm birth, small for gestational age and birth weight. Summary data for HIGH versus LOW (or NONE), ANY (Regular) versus NONE, and ONE EXTRA CUP/DAY coffee consumption are displayed in, Figure 10 Figure 11 and Figure 12 respectively which show the meta-analyses selected as highest form of evidence for coffee consumption and each outcome. These show risk estimates for each outcome from most harmful association (top) to most beneficial association (bottom) and includes the number of studies, events, total subjects, effects model, tau-squared, I^2, Eggers, and AMSTAR score. Associations with decaffeinated coffee consumption across the three exposure categories are displayed in Figure 13 and interventional exposures for coffee versus control, for outcomes of blood pressure, lipids and pregnancy-related outcomes are displayed in Figure 14.

The exposure of HIGH versus LOW (or NO) coffee consumption was the most frequently studied exposure and statistical significance was reached in beneficial associations with 19 health outcomes and harmful associations with six. The remaining 34 outcomes were either negatively or positively associated but without reaching statistical significance. Similarly, comparing ANY coffee (Regular) with NONE, statistical significance was reached in beneficial associations with 11 outcomes and harmful associations with three. Finally, for ONE EXTRA CUP/DAY consumption, statistical significance was reached in beneficial associations with 11 outcomes and harmful associations with three. Eight out of 18 studies[127–135] that tested for non-linearity for the cup/day association found significant statistical evidence for this.

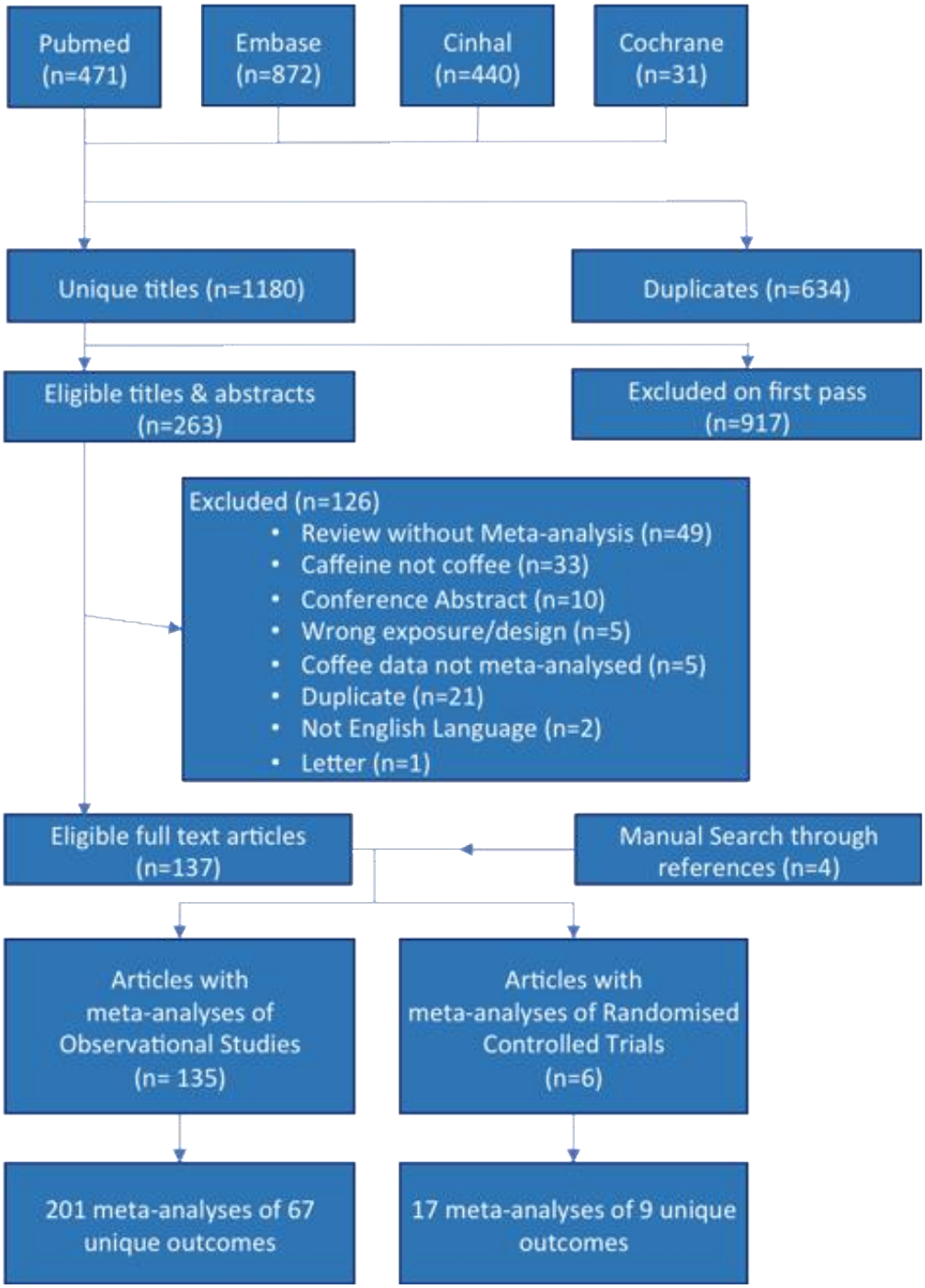


Figure 9: Flowchart of selection of studies for inclusion in the umbrella review on coffee consumption and health outcomes

Outcome	Author	Year	Events/total pop	Years	Measure	Risk Estimate	Estimat	LCL	UCL	Total	Cohort	CC	Model	Tau²	I²	Eggers	AMSTAR
Acute Leuk. in Child.[136] *	Thomopo	2015	2453/4975	N/A	OR		1.57	1.16	2.11	6	0	6	R	0.06	55.17	ND	5
Lung Cancer[137]*	Xie	2016	540/84984	10-23	OR		1.56	1.12	2.17	5	5	0	R	0.06	44.72	ND	3
Pregnancy Loss[131]*	Li	2015	12311/155831	N/A	OR		1.46	1.06	1.99	5	5	0	R	0.11	86.50	ND	5
Rheumatoid Arth.[138,139]*	Lee	2015	764/132677	11-20	RR		1.31	0.97	1.77	3	3	0	R	0.00	0.00	ND	4
Low Birth Weight[140]*	Rhee	2015	2133/42036	N/A	OR		1.31	1.03	1.67	2	2	0	R	0.00	0.00	ND	7
Lymphoma[141]*	Wang	2016	209/89897	6-12	RR		1.23	0.75	2.02	3	3	0	R	0.00	0.00	ND	5
Laryngeal Cancer[142]*	Ouyang	2014	2596/NP	NP	RR		1.22	0.92	1.62	8	1	7	R	0.10	74.08	ND	6
1st Tri Preterm Birth[143]	Maslova	2010	NP	N/A	OR		1.22	1.00	1.49	NP	NP	NP	F	NP	NP	NP	3
3rd Tri Preterm Birth[143]	Maslova	2010	NP	N/A	OR		1.22	0.95	1.57	NP	NP	NP	F	NP	NP	NP	3
Oral Cleft Malf. [144]*	Browne	2006	627/56953	2	OR		1.21	0.92	1.59	3	1	2	R	0.00	0.00	ND	2
Bladder Cancer[141]*	Wang	2016	1563/340544	6-22	RR		1.21	0.94	1.55	10	10	0	R	0.06	39.94	<0.01	5
Cardiovascular Malf[144].	Browne	2006	4068/60427	2	OR		1.16	0.90	1.5	4	1	3	R	0.03	47.94	ND	2
Gastric Cancer[141]*	Wang	2016	3317/1305447	4-18	RR		1.15	0.96	1.37	12	12	0	R	0.04	49.01	0.99	5
Hip Fracture[145]*	Li	2015	5408/205930	4-30	RR		1.13	0.86	1.48	9	9	0	R	0.11	79.44	0.02	4
2nd Tri Preterm Birth[143]	Maslova	2010	NP	N/A	OR		1.12	1.02	1.22	NP	NP	NP	F	NP	NP	NP	3
Hypertension[146]*	Zhang	2011	37135/172567	6-33	RR		1.08	0.96	1.21	6	6	0	R	0.01	37.34	ND	5
Ovarian Cancer[141]*	Wang	2016	3026/687017	6-14	RR		1.08	0.91	1.28	9	9	0	R	0.02	24.14	ND	5
Cancer Mortality[147a]	Grosso	2016	40991/916857	6-26	RR		1.07	0.98	1.16	15	15	0	R	NP	42	NP	5
GORD[148]*	Kim	2013	12816/76792	N/A	OR		1.06	0.94	1.19	15	0	15	R	0.03	66.14	0.04	7
Rectal Cancer[128]*	Gan	2016	5878/1751343	4-18	RR		1.06	0.95	1.19	15	15	0	R	0.01	13	0.90	7
Coronary Heart Dis.[127b]*	Ding	2014	28347/996286	3-32	RR		1.01	0.86	1.18	23	23	0	R	0.12	83.41	0.84	8
Thyroid Cancer[149]*	Han	2017	265/197841	NP	OR		1.00	0.75	1.33	2	2	0	R	0.00	0.00	ND	4
Fracture[150]*	Lee	2014	9429/233907	6-30	RR		0.99	0.86	1.14	9	9	0	R	0.02	68.91	0.12	7

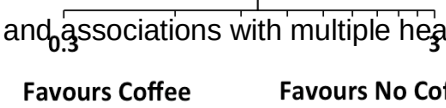
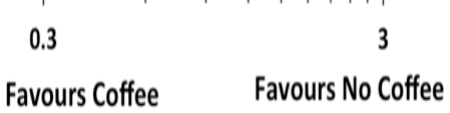


Figure 10: Coffee exposure of HIGH versus LOW and associations with multiple health outcomes

Outcome	Author	Year	Events/total pop	Years	Measure	Risk Estimate	Estimat	LCL	UCL	Total	Cohort	CC	Model	Tau²	I²	Eggers	AMSTAR
Breast Cancer[141]*	Wang	2016	29178/997482	5-26	RR		0.99	0.94	1.03	17	17	0	R	0.00	0.00	0.74	5
Pancreatic Cancer[151]*	Nie	2016	4185/1824386	NP	RR		0.99	0.8	1.21	20	20	0	R	0.09	48.26	0.68	5
Glioma[152]*	Malerba	2013	184/1669442	8-24	RR		0.98	0.79	1.23	4	4	0	R	0.00	6.41	ND	5
Cardiovascular Dis.[127b]*	Ding	2014	47779/1283685	3-32	RR		0.98	0.89	1.07	35	35	0	R	0.07	76.39	0.89	8
Cognitive Decline[153]*	Liu	2016	NP/29155	1-28	RR		0.97	0.85	1.11	11	11	0	R	0.02	24.20	0.73	6
Heart Failure[132b]*	Mostofsky	2012	6522/140220	8-35	RR		0.96	0.86	1.07	5	5	0	R	0.00	0.00	ND	6
Atrial Fibrillation[154]*	Larsson	2015	10406/248910	9-27	RR		0.96	0.84	1.08	5	5	0	R	0.01	60.93	ND	5
Colorectal Cancer[141]*	Wang	2016	23289/2141185	4-18	RR		0.96	0.89	1.04	21	21	0	R	0.01	24.41	0.70	5
Stroke[127b]*	Ding	2014	12030/670223	3-32	RR		0.96	0.83	1.11	15	15	0	R	0.03	53.20	0.09	8
CVD Mortality[147a]	Grosso	2016	34574/1254508	6-21	RR		0.95	0.85	1.06	23	23	0	R	NP	92	NP	5
Venous TE[155]*	Lippi	2015	4215/65951	12-19	RR		0.93	0.73	1.20	2	2	0	R	0.01	30.87	ND	3
Colon Cancer[128b]*	Gan	2017	13075/1781564	4-18	RR		0.92	0.83	1.02	16	16	0	R	0.01	29.92	0.89	7
Metabolic Syndrome[134]*	Shang	2015	29828[c]/106855	NP	RR		0.91	0.86	0.95	3	3	0	R	0.00	0.00	ND	6
All-cause Mortality[147a]*	Grosso	2016	183991/1610543	6-28	RR		0.90	0.85	0.96	24	24	0	R	NP	83	NP	5
Prostate cancer*	Wang	2016	37362/864012	6-28	RR		0.88	0.81	0.96	14	14	0	R	0.01	30.82	0.51	5
Depression[81]*	Grosso	2016	5253/327697	NP	RR		0.88	0.79	0.99	3	3	0	R	0.01	44.27	ND	8
CHD Mortality[29a]	Grosso	2016	NP	NP	RR		0.88	0.65	1.20	12	12	0	R	NP	95	NP	5
Oesophageal Cancer[141]*	Wang	2016	1068/1395309	6-17	RR		0.86	0.71	1.04	6	6	0	R	0.00	0.00	ND	5
Stroke Mortality[147a]	Grosso	2016	NP	NP	RR		0.85	0.69	1.03	9	9	0	R	NP	89	NP	5
Gallstones[133b]*	Zhang	2015	11282/226432	NP	RR		0.83	0.76	0.89	7	7	0	R	0.00	35.92	ND	2
All cancer[156]	Yu	2011	34177/2179126	14.3	RR		0.82	0.74	0.89	40	40	0	R	NP	67.7	0.79	5
Non-Melanoma SC[157]*	Caini	2017	33332/NP	NP	RR		0.82	0.74	0.92	4	4	0	R	0.01	55.42	ND	5
Renal Cancer[141]*	Wang	2016	977/1036465	6-14	RR		0.79	0.54	1.16	5	5	0	R	0.08	49.74	ND	5

Outcome	Author	Year	Events/total pop	Years	Measure	Risk Estimate	Estimat	LCL	UCL	Total	Cohort	CC	Model	Tau²	I²	Eggers	AMSTAR
Endometrial Cancer[158]*	Zhou	2015	10100/1534039	9-26	RR		0.76	0.69	0.84	13	13	0	R	0.01	28.54	0.03	7
Melanoma[159]*	Yew	2016	3327/925484	NP	RR		0.76	0.64	0.91	9	9	0	R	0.03	48.34	0.77	8
Alzheimer's Disease[153]*	Liu	2016	NP/NP	5-21	RR		0.73	0.55	0.97	4	4	0	R	0.00	0.00	ND	6
Type II diabetes[129b*]	Ding	2014	45335/1109272	1-24	RR		0.70	0.65	0.75	27	27	0	R	0.01	50.28	0.05	7
Oral Cancer[141]*	Wang	2016	1910/1395309	6-26	RR		0.69	0.48	0.99	6	6	0	R	0.12	73.67	ND	5
Cirrhosis[160]*	Liu	2015	1785/130305	NP	OR		0.69	0.44	1.07	3	3	0	R	0.02	12.91	ND	7
Renal Stones[161]*	Wang	2014	NP/126382	NP	RR		0.67	0.56	0.81	2	2	0	R	0.00	0.00	ND	6
Parkinson's Disease[130b]*	Qi	2014	2414/894568	NP	RR		0.64	0.53	0.76	7	7	0	R	0.01	15.88	ND	5
Leukaemia[156]	Yu	2011	NP[d]	8-11	RR		0.63	0.41	0.84	2	2	0	R	NP	0	NP	5
Post MI Mortality[162]*	Brown	2016	604/3271	3.8	RR		0.55	0.45	0.67	2	2	0	R	0.00	8.91	ND	4
Gout[163]*	Park	2016	NP/135302	NP	RR		0.50	0.36	0.70	2	2	0	R	0.02	34.90	ND	6
Liver Cancer[164]*	Bravi	2016	3414/2267143	10-44	RR		0.50	0.43	0.58	11	11	0	R	0.01	20.00	0.62	6
Chronic Liver Dis.[164]*	Bravi	2016	1410/386049	6-19	RR		0.35	0.22	0.56	5	5	0	R	0.20	75.32	ND	6



*Estimates are from our own re-analysis

[a] Maximum consumption in a non-linear dose-response analysis

[b] p-value for non-linearity significant

[c] Not all no. of cases published;

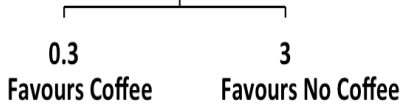
[d] Not possible to separate from other outcomes

NP = Not published; ND = Not done N/A = Not appropriate

Mortality | Cardiovascular | Cancer | Metabolic | Liver & GI | Renal | Pregnancy | Musculoskeletal | Neurological | Gynaecological

Figure 11: Coffee exposure of ANY versus NONE and associations with multiple health outcomes

Outcome	Author	Year	Events/total pop	Years	Measure	Risk Estimate	Estimate	LCL	UCL	Total	Cohort	CC	Model	Tau²	I²	Eggers	AMSTAR
Acute Leuk. Child.[165,166]	Yan	2015	NP	N/A	OR		1.44	1.07	1.92	3	0	3	F	NP	41.8	0.33	4
Lymphoma[167]*	Han	2016	219/124131	NP	RR		1.29	0.92	1.8	3	3	0	R	0.04	17.63	ND	7
Lung Cancer[168]*	Galarrag	2016	11145/NP	NP	RR		1.28	1.12	1.47	8	8	0	R	0.02	86.79	ND	5
Urinary Tract Cancer[169]	Zeegers	2001	NP	NP	OR		1.18	1.01	1.38	14	0	14	R	NP	NP	0.51	6
Endometriosis[170]*	Chiaffarin	2014	387/385	NP	RR		1.13	0.46	2.76	3	1	2	R	0.43	69.98	ND	5
Hypertension[171]*	Steffen	2012	36178/1246388	6-33	RR		1.03	0.98	1.08	4	4	0	R	0.00	73.48	ND	6
Gastric Cancer[172]*	Fang	2015	1535/255112	2-25	RR		1.02	0.79	1.31	8	8	0	R	0.07	57.65	ND	7
Rectal Cancer[173]	Galeone	2010	4594/NP	N/A	OR		0.98	0.85	1.13	10	0	10	R	NP	71.20	NP	4
Breast Cancer[156]*	Yu	2011	NP[d]	8-24	RR		0.95	0.9	1.01	11	11	0	R	0.00	19.92	0.58	5
Venous TE[155]*	Lippi	2015	4215/65951	12-19	RR		0.94	0.82	1.07	2	2	0	R	0.00	0.00	ND	3
Glioma[152]*	Malerba	2013	1194/3995802pym	8-24	RR		0.93	0.76	1.14	3	3	0	R	0.01	43.45	ND	5
Colon Cancer[173]*	Galeone	2010	7537/NP	N/A	OR		0.93	0.81	1.07	11	0	11	R	NP	81.7	NP	4
Thyroid Cancer[174]	Mack	2003	1653/2967	N/A	OR		0.89	0.72	1.1	9	0	9	R	0.02	21.04	ND	2
Stroke[175]*	Zhang	2012	12414/492760	2-25	RR		0.89	0.81	0.97	13	13	0	R	0.01	69.18	0.23	6
Bladder Cancer[156]*	Yu	2011	NP[d]	6-13	RR		0.89	0.79	1.01	9	9	0	R	0.00	0.00	ND	5
Liver Cirrhosis[160]*	Liu	2015	1880/130496	NP	OR		0.89	0.73	1.08	3	3	0	R	0.00	0.00	ND	7
Prostate Cancer[176]*	Cao	2013	8973/206096	5-34	RR		0.88	0.81	0.96	10	10	0	R	0.00	31.93	0.11	5
Cancer[156]	Yu	2011	34177/2179126	14.3	RR		0.87	0.82	0.92	40	40	0	R	NP	78.1	0.79	5
Neural Tube Defects[177]*	Li	2015	2077/NP	NP	OR		0.86	0.51	1.45	7	1	6	R	0.39	86.36	ND	7
Endometrial Cancer[178]*	Bravi	2009	201/1513	10-15	RR		0.86	0.51	1.45	2	2	0	R	0.11	73.23	ND	4
Colorectal Cancer[173]	Galeone	2010	9568/NP	N/A	OR		0.83	0.73	0.95	13	0	13	R	NP	80.00	NP	4
UrinaryIncontinence[179]*	Sun	2016	7284/47518	NP	OR		0.75	0.54	1.04	3[e]	1	0	R	0.08	93.11	ND	6
Alzheimer's Disease[180]*	Barranco	2007	454/5497	NP	RR		0.73	0.54	0.99	2	2	0	R	0.00	0.00	ND	3



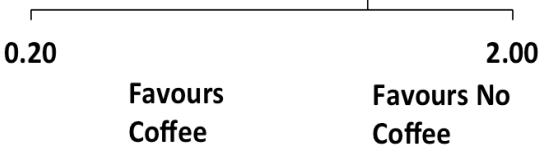
Outcome	Author	Year	Events/total pop	Years	Measure	Risk Estimate	Estimate	LCL	UCL	Total	Cohort	CC	Model	Tau²	I²	Eggers	AMSTAR
Liver Fibrosis[160]*	Liu	2015	1414/3738	NP	OR		0.73	0.56	0.94	7	7	0	R	0.08	81.11	ND	7
CKD[181]*	Wijarnpreecha	2016	NP/14898	n/a	RR		0.71	0.47	1.08	4[e]	0	0	R	0.11	65.98	ND	7
NAFLD[105]*	WijarNPreecha	2017	NP/2407	NP	RR		0.71	0.6	0.85	3[e]	1	1	R	0.00	0.00	ND	7
Liver Cancer[164]*	Bravi	2016	3414/2267143	10-44	RR		0.66	0.55	0.78	12	12	0	R	0.06	79.84	0.24	6
Parkinson's Disease[182]*	Noyce	2012	1940/719187	10-27	RR		0.64	0.53	0.77	6	6	0	R	0.02	29.00	ND	7
Chronic Liver Dis.[164]*	Bravi	2016	1463/437355	6-19	RR		0.62	0.47	0.82	6	6	0	R	0.07	80.25	ND	6

*Estimates are from our own re-analysis
[d] Not possible to separate from other outcomes
[e] Included cross-sectional studies
NP = Not published
ND = Not done

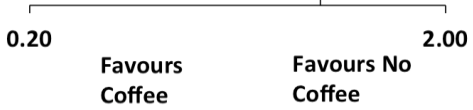
Mortality | Cardiovascular | Cancer | Metabolic | Liver & GI | Renal | Pregnancy | Musculoskeletal | Neurological | Gynaecological

Figure 12: Coffee consumption of ONE EXTRA CUP/DAY and associations with multiple health outcomes

Outcome	Author	Year	No. of events	Follow	Summary	Risk Estimate	Estimat	LCL	UCL	Total	Cohort	Case	Effects	Tau²	I²	Eggers	AMSTA
Low Birth Weight[183]	Chen	2014	738/12632	N/A	RR		1.16	0.91	1.48	2	1	1	R	NP	91.9	NP	7
Lung Cancer[168]	Galarraga	2016	19892/623645	NP	RR		1.04	1.03	1.05	21	8	13	R	NP	75.1	<0.001	5
Pregnancy Loss[131b]	Li	2015	11951/153259	N/A	OR		1.04	1.03	1.05	6	4	2	R	NP	NP	NP	5
Bladder Cancer[184]	Wu	2015	753/236343	10-22	OR		1.03	0.99	1.06	6	0	0	R	NP	*44*	NP	8
Fracture[185]	Liu	2012	9597/214059	NP	RR		1.03	1.00	1.06	10	10	0	R	NP	80.9	NP	6
Gastric Cancer[186]	Zeng	2015	2019/1289314	10-18	RR		1.02	0.98	1.07	9	9	0	R	NP	57	0.1	7
Ovarian Cancer[187]	Braem	2012	1992/313195	NP	HR		1.02	0.99	1.05	6	6	0	R	NP	NP	NP	6
Alzheimer's Disease[153]	Liu	2016	NP/NP	5-21	RR		1.02	0.95	1.08	2	2	0	R	NP	16	NP	6
Rectal Cancer[128]	Gan	2017	5812/1751343	4-18	RR		1.01	0.99	1.03	14	14	0	F	NP	11	0.38	8
Glioma[152]	Malerba	2012	1361/4777317pym	8-24	RR		1.01	0.96	1.07	3	3	0	R	NP	52.2	>0.25	6
Cancer Mortality[188]	Malerba	2013	NP	7-25	RR		1.00	0.99	1.01	9	9	0	R	NP	NP	NP	6
Oesophageal Cancer[189]	Zheng	2013	NP	NP	OR		1.00	0.94	1.06	NP	NP	NP	NP	NP	NP	NP	5
Hip Fracture[190]	Li	2013	857/138009	NP	RR		1.00	0.96	1.03	4	4	0	NP	NP	NP	NP	5
Cognitive Decline[153]	Liu	2016	NP/29155	5-21	RR		1.00	0.98	1.02	8	8	0	R	NP	0	NP	6
Breast Cancer[191]	Li	2013	TBC	4-24	RR		0.99	0.98	1.00	15	15	0	R	NP	0	NP	6
Atrial Fibrillation[154]	Larsson	2015	10406/248910	9-27	RR		0.99	0.97	1.01	6	6	0	R	NP	65.7	≥0.43	5
Pancreatic Cancer[192]	Ran	2016	1281/568428	6-36	RR		0.99	0.96	1.03	10	10	0	R	NP	NP	NP	4
Colorectal Cancer[128b]	Gan	2017	22034/1872460	4-18	RR		0.99	0.98	1.01	17	17	0	R	NP	34.3	0.43	8
Colon Cancer[128b]	Gan	2017	12872/1781564	4-18	RR		0.98	0.97	1.00	15	15	0	F	NP	23	0.86	8
Prostate Cancer[141]	Wang	2016	36217/797412	6-28	RR		0.98	0.97	0.99	10	10	0	R	NP	NP	NP	5
CVD Mortality[188]	Malerba	2013	NP	7-25	RR		0.98	0.95	1.00	16	16	0	R	NP	87.8	NP	6
All cancer[156]	Yu	2011	34177/2179126	14.3	RR		0.97	0.96	0.98	40	40	0	R	NP	78.1	NP	5
Melanoma[193]	Wang	2015	6094/690688	6-28	RR		0.97	0.93	1.00	7	6	1	R	NP	NP	NP	7



Outcome	Author	Year	Events/total pop	Years	Measure	Risk Estimate	Estimat	LCL	UCL	Total	Cohort	CC	Model	Tau²	I²	Eggers	AMSTA
Renal Cancer[194]	Huang	2014	120/174028	6-23	RR		0.97	0.75	1.26	4	4	0	F	NP	NP	NP	4
All-Cause Mortality[135b]	Je	2014	124011/947047	7-25	RR		0.96	0.94	0.97	16	16	0	R	NP	NP	NP	6
Gallstones[133b]	Zhang	2015	10911/198831	NP	RR		0.95	0.91	1.00	3	3	0	R	NP	54.5	NP	8
Type II diabetes[195]	Jiang	2014	46722/974372	2-20	RR		0.94	0.93	0.95	20	20	0	R	NP	NP	NP	8
Endometrial Cancer[141]	Wang	2016	4730/592672	6-26	RR		0.94	0.92	0.96	11	11	0	NP	NP	NP	NP	5
Depression[196]	Wang	2016	14506/327608	NP	RR		0.92	0.87	0.97	5[e]	2	1	R	NP	60.4	0.03	6
Renal Stones[161]	Wang	2014	NP/167650	NP	RR		0.91	0.88	0.95	5	3	2	R	NP	42.7	0.18	6
Parkinson's Disease[197]	Hernan	2002	459/187281	NP	RR		0.88	0.77	1.00	4	4	0	R	NP	NP	NP	4
Liver Cancer[164]	Bravi	2016	3414/2267143	10-44	RR		0.85	0.81	0.90	12	12	0	R	NP	NP	0.17	6
Cirrhosis[198]	Kennedy	2016	1364/427687	14-18	RR		0.77	0.64	0.87	5	5	0	R	NP	91.1	NP	9
Cirrhosis Mortality[198]	Kennedy	2016	1034/303622	14-18	RR		0.74	0.59	0.86	4	4	0	R	NP	90.3	NP	9
Chronic Liver Dis.[164]	Bravi	2016	1463/437355	10-44	RR		0.74	0.65	0.83	6	6	0	R	NP	NP	043	6

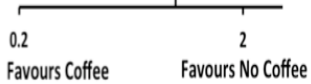


Nb: No dose response analyses were re-analysed
[b] p-value for non-linearity significant
[c] Not all no. of cases published;
[d] Not possible to separate from other outcomes
[e] Included cross-sectional studies
NP = Not published
ND = Not done; N/A = Not appropriate

Mortality | Cardiovascular | Cancer | Metabolic | Liver & GI | Renal | Pregnancy | Musculoskeletal | Neurological | Gynaecological

Figure 13: Decaffeinated coffee exposure and associations with multiple health outcomes

Outcome	Author	Year	Events/total pop	Years	Measure	Risk Estimate	Estimate	LCL	UCL	Total	Cohort	CC	Model	Tau²	I²	Eggers	AMSTAR
ANY versus NONE																	
Urinary Tract Cancer[169]	Zeegers	2001	NP	N/A	OR		1.18	0.99	1.4	4	0	4	R	NP	2.4	0.51	5
HIGH versus LOW																	
RheumatoidArthritis[138,139]*	Lee	2014	638/113822	11-20	RR		1.71	0.79	3.71	2	2	0	R	NP	71.2	NP	5
Bladder Cancer[184]	Wu	2015	NP	10-22	OR		1.29	0.88	1.89	5	NP	NP	R	NP	62.7	NP	8
Coronary Heart Dis.[199]	Sofi	2007	5838/155805	14-20	RR		1.1	0.9	1.34	3	3	0	R	NP	NP	NP	4
NM Skin Cancer[157]*	Caini	2017	25413/NP	NP	RR		1.01	0.94	1.1	3	3	0	R	0	0	ND	5
Cardiovascular Dis.[127]	Ding	2014	NP	NP	RR		1.00	0.88	1.14	5	5	0	R	NP	NP	NP	7
Cancer Mortality[147a]	Grosso	2016	NP	NP	RR		1.00	0.91	1.09	2	2	0	R	NP	NP	NP	5
Breast Cancer[200]	Jiang	2013	32790/404188	10-22	RR		0.97	0.89	1.06	12	4	8	F	NP	29.7	NP	5
Parkinson's Disease[130]	Qi	2015	1210/251300	NP	RR		0.94	0.78	1.12	4	3	1	NP	NP	NP	NP	6
MalignantMelanoma[201]*	Liu	2016	NP	NP	RR		0.94	0.82	1.08	5	5	0	R	NP	0	0.116	7
All-cause Mortality[147a]	Grosso	2016	NP	NP	RR		0.90	0.79	1.01	5	5	0	R	NP	NP	NP	5
CVD Mortality[147a]	Grosso	2016	NP	NP	RR		0.86	0.69	1.08	3	3	0	R	NP	NP	NP	5
Type II Diabetes[129*b]	Ding	2014	22015/417454	1-24	RR		0.80	0.70	0.91	11	11	0	R	0.03	62	0.13	7
Endometrial Cancer[158]	Zhou	2015	3127/363254	9-26	RR		0.77	0.63	0.94	4	4	0	R	NP	0	0.88	7
Lung Cancer[202]	Tang	2010	NP	NP	RR		0.66	0.54	0.81	2	NP	NP	R	NP	0	NP	5
EXTRA 1 CUP/DAY																	
Endometrial Cancer[158]	Zhou	2015	3127/363254	9-26	RR		0.96	0.92	0.99	9	9	0	R	NP	NP	NP	7
Type II Diabetes[129]	Ding	2014	22015/417454	1-24	RR		0.94	0.91	0.98	14	16	0	R	NP	NP	NP	7
Liver Cancer[103]	Kennedy	2017	800/750000	11-18	RR		0.93	0.86	1.00	3	0	0	R	NP	NP	NP	8



*Estimates from our own reanalysis
[a] Maximum consumption in a non-linear dose-response analysis
[b] p-value for non-linearity significant
NP = Not published; ND = Not done; N/A = Not appropriate

Mortality | Cardiovascular | Cancer | Metabolic | Liver & GI | Renal | Pregnancy | Musculoskeletal | Neurological | Gynaecological

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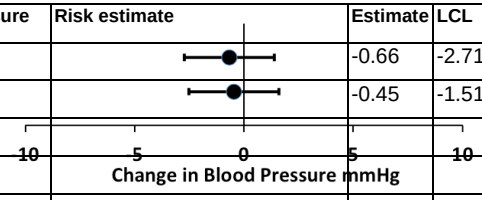
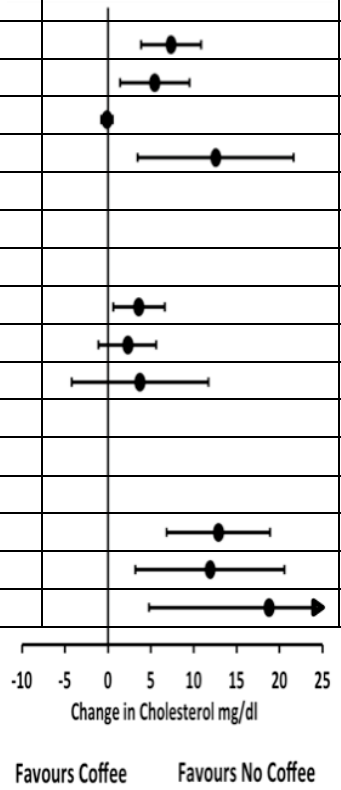
Figure 14: Coffee consumption in randomised controlled trials and multiple health outcomes

Outcome	Author	Year	N	Duration	Dose cups	Measure	Risk estimate	Estimate	LCL	UCL	Studies	Model	Tau²	I²	Eggers	AMSTAR
Systolic Blood Press. [171]*	Steffen	2012	1466	62 days	2.0 to ≥5	MD		-0.66	-2.71	1.39	12	R	6.90	72	NP	6
Diastolic Blood Press.[171]*	Steffen	2012	1466	62 days	2.0 to ≥5	MD		-0.45	-1.51	0.61	12	R	1.25	41	NP	6
Total Cholesterol[203]*	Cai	2012	1017	45 days	2.4 to 8.0	MD		7.36	3.85	10.87	12	R	NP	67.3	0.01	6
LDL-Cholesterol[203]*	Cai	2012	NP	45 days	2.4 to 8.0	MD		5.44	1.38	9.51	7	R	NP	58.4	0.4	6
HDL-Cholesterol[203]*	Cai	2012	NP	45 days	2.4 to 8.0	MD		-0.11	-0.76	0.54	9	F	NP	21.6	0.62	6
Triglyceride[203]*	Cai	2012	NP	45 days	2.4 to 8.0	MD		12.55	3.47	21.64	6	R	NP	66.4	0.23	6
Filtered coffee																
Total Cholesterol[203]	Cai	2012	NP	45 days	2.4 to 8.0	MD		3.60	0.60	6.60	7	F	NP	0	NP	6
LDL-Cholesterol[203]	Cai	2012	NP	45 days	2.4 to 8.0	MD		2.30	-1.10	5.60	3	F	NP	10.4	NP	6
Triglyceride[203]	Cai	2012	NP	45 days	2.4 to 8.0	MD		3.70	-4.20	11.70	3	F	NP	0	NP	6
Unfiltered coffee																
Total Cholesterol[203]	Cai	2012	NP	45 days	2.4 to 8.0	MD		12.90	6.80	18.90	5	R	NP	79.3	NP	6
LDL-Cholesterol[203]	Cai	2012	NP	45 days	2.4 to 8.0	MD		11.90	3.20	20.60	5	R	NP	73.3	NP	6
Triglyceride[203]	Cai	2012	NP	45 days	2.4 to 8.0	MD		18.80	4.80	32.70	5	R	NP	77.1	NP	6





Outcome	Author	Year	N	Duration	Dose cups	Measure	*Risk estimate*	Estimate	LCL	UCL	Studies	Model	Tau²	I²	Eggers	AMSTA
Caffeinated coffee																
Total Cholesterol[203]	Cai	2012	NP	45 days	2.4 to 8.0	MD		9.20	5.00	13.40	12	R	NP	70.7	NP	6
LDL-Cholesterol[203]	Cai	2012	NP	45 days	2.4 to 8.0	MD		5.50	0.80	10.20	7	R	NP	62.8	NP	6
Triglyceride[203]	Cai	2012	NP	45 days	2.4 to 8.0	MD		13.80	3.70	24.00	6	R	NP	68.7	NP	6
Decaffeinated coffee																
Total Cholesterol[203]	Cai	2012	NP	45 days	2.4 to 8.0	MD		3.50	-1.10	8.10	3	F	NP	0	NP	6
LDL-Cholesterol[203]	Cai	2012	NP	45 days	2.4 to 8.0	MD		6.30	-0.80	13.40	2	F	NP	8.7	NP	6
Triglyceride[203]	Cai	2012	NP	45 days	2.4 to 8.0	MD		3.50	-10.60	17.70	1	N/A	NP	N/A	N/A	6
							-11 -6 -1 4 9 14 19 24									
							Change in Cholesterol mg/dl									
							Favours Coffee Favours No Coffee									
Preterm Birth[204]	Jahanfar	2015	1153	140 days	3.0	RR		0.81	0.48	1.37	1	N/A	N/A	N/A	N/A	9
Small for gest. age[204]	Jahanfar	2015	1150	140 days	3.0	RR		0.97	0.57	1.64	1	N/A	N/A	N/A	N/A	9
							0.3 Risk Estimate 3									
							Favours Coffee Favours No Coffee									
Birth weight[204]	Jahanfar	2015	1197	140 days	3.0	MD		20.00	-48.70	88.68	1	N/A	N/A	N/A	N/A	9
							-60.00 -10.00 40.00 90.00									
							Mean difference in birth weight (g)									
							Favours Coffee Favours No Coffee									

*Estimates are from our own re-analysis

NP = Not Published; N/A = Not Appropriate, MD=Mean Difference

Mortality | Cardiovascular | Cancer | Metabolic | Liver & GI | Renal | Pregnancy | Musculoskeletal | Neurological | Gynaecological

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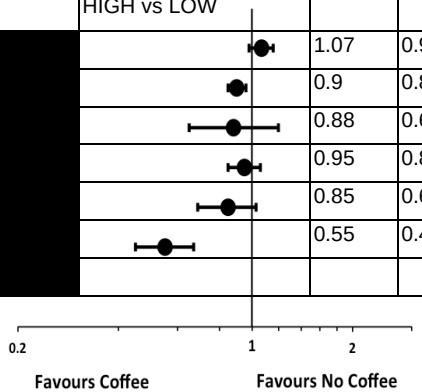
2.3.1 All-cause Mortality

In the most recent meta-analysis by Grosso et al, summary estimates indicated largest relative risk reduction associated with the consumption of 3 cups/day (RR 0.83 (95%CI 0.79 to 0.88) compared with no coffee consumption. The highest exposure category (7 cups per day) was associated with a 10% lower risk of all-cause mortality (RR 0.90 (95%CI 0.85 to 0.96))[147]. Stratification by gender produced similar results. Despite a significant test for non-linearity ($p<0.001$), authors of a separate article performed a linear dose-response analysis and found coffee consumption of ONE EXTRA CUP/DAY was associated with a 4% lower risk of all-cause mortality (RR 0.96 (95%CI 0.94 to 0.97))[135]. The apparent beneficial association between coffee and all-cause mortality was consistent across all meta-analyses. Decaffeinated coffee was also beneficially associated with lower all-cause mortality with summary estimates indicating largest benefit at 3 cups/day (RR 0.89 (95%CI 0.85 to 0.89))[147] in a non-linear dose-response analysis.

A summary of associations between coffee consumption and mortality across different categories of exposure is shown in Figure 15.

Figure 15: Coffee consumption and mortality outcomes

Outcome	Risk Estimate	Estimate	LCL	UCL	Risk Estimate	Estimate	LCL	UCL	Risk Estimate	Estimate	LCL	UCL
	HIGH vs LOW				ANY vs NONE				1 EXTRA CUP			
Cancer Mortality		1.07	0.98	1.16						1.00	0.99	1.01
All-Cause Mortality		0.9	0.85	0.96						0.96	0.94	0.97
CHD Mortality		0.88	0.65	1.20								
CVD Mortality		0.95	0.85	1.06						0.98	0.95	1
Stroke Mortality		0.85	0.69	1.03								
Post MI Mortality		0.55	0.45	0.67								
Cirrhosis Mortality										0.74	0.59	0.86



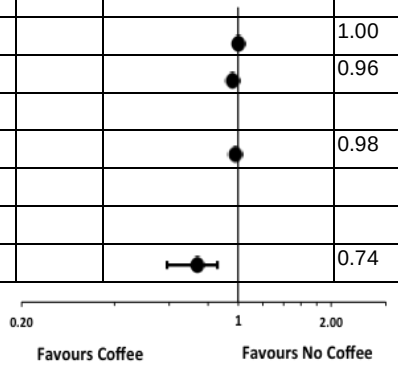
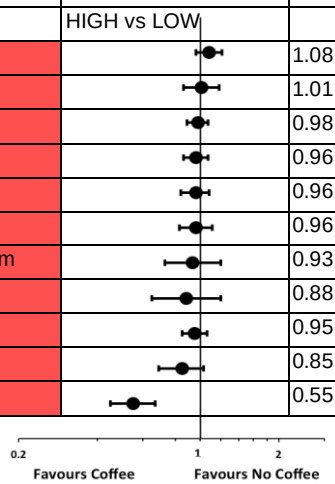
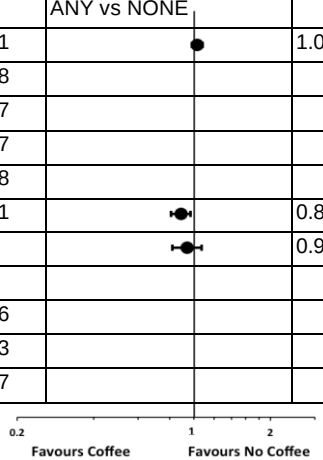
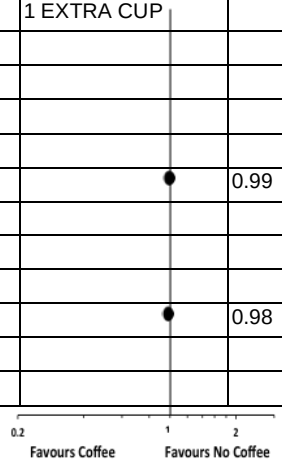


Figure 16: Coffee consumption and cardiovascular outcomes

Outcome	Risk Estimate	Estimate	LCL	UCL	Risk Estimate	Estimate	LCL	UCL	Risk Estimate	Estimate	LCL	UCL
	HIGH vs LOW				ANY vs NONE				1 EXTRA CUP			
Hypertension		1.08	0.96	1.21		1.03	0.98	1.08				
Coronary Heart Disease		1.01	0.86	1.18								
Cardiovascular Disease		0.98	0.89	1.07								
Heart Failure		0.96	0.86	1.07								
Atrial Fibrillation		0.96	0.84	1.08						0.99	0.97	1.01
Stroke		0.96	0.83	1.11		0.89	0.81	0.97				
Venous Thromboembolism		0.93	0.73	1.2		0.94	0.82	1.07				
CHD Mortality		0.88	0.65	1.2								
CVD Mortality		0.95	0.85	1.06						0.98	0.95	1
Stroke Mortality		0.85	0.69	1.03								
Post MI Mortality		0.55	0.45	0.67								







2.3.2 Cardiovascular Disease

Coffee consumption was consistently associated with lower risk of mortality from all cardiovascular disease (CVD) causes, coronary heart disease (CHD) and stroke in a non-linear relationship. Summary estimates indicated the largest relative risk reduction at 3 cups/day[147] with risks reduced by 19% (RR 0.81 (95% CI 0.72 to 0.90)) for CVD mortality, 16% (0.84 (95% CI 0.71 to 0.99)) for CHD mortality, and 30% (RR 0.70 (95% CI 0.57 to 0.86)) for stroke mortality. The beneficial effect was less pronounced at consumption above 3 cups/day but was not associated with harm and the estimates did not reach statistical significance at the highest intakes. Women appeared to benefit more than men at higher coffee consumption for outcomes of CVD and CHD mortality, but less so for stroke mortality[147]. In a separate meta-analysis, that didn't test for non-linearity, an exposure of ONE EXTRA CUP/DAY was associated with a 2% reduced risk of cardiovascular mortality (RR 0.98 (95%CI 0.95 to 1.00))[188]. There was also evidence of benefit in relation to HIGH versus LOW coffee consumption after myocardial infarction and lower risk of mortality (HR 0.55 (95% CI 0.45 to 0.67))[162].

Incident cardiovascular disease (RR 0.85 (95% CI 0.80 to 0.90)), coronary heart disease (RR 0.90 (95% CI 0.84 to 0.97)), and stroke (RR 0.80 (95% CI 0.75 to 0.86)) also appeared to have lower risk associated with coffee consumption in a non-linear relationship. Summary estimates indicated largest benefits at consumptions of 3-5 cups/day[127]. Gender did not appear to modify the associations. Risk was also lower for the comparison of HIGH versus LOW consumption but did not reach statistical significance. ANY coffee versus NONE appeared to reduce the risk of stroke (RR 0.89 (95% CI 0.81 to 0.97))[175]. HIGH versus LOW coffee consumption and ONE EXTRA CUP/DAY exposures were both associated with lower risk of atrial fibrillation but neither reached statistical significance[205]. There was no statistically significant association between coffee consumption and risk of venous thromboembolism[155]. There was a non-linear association between coffee consumption and heart failure with summary estimates indicating largest benefit at 4 cups/day (RR 0.89 (95% CI 0.81 to 0.99))[132] with slightly higher risk of heart failure at very high consumption of 10 or more cups per day (RR 1.01 (95% CI 0.90 to 1.14)) although this did not reach statistical significance[132]. A diagnosis of hypertension was not associated with any level of coffee consumption in a non-linear dose-response

analysis[146] nor when comparing ANY with NONE[171]. There was no clear benefit when comparing HIGH to LOW decaffeinated consumption and CVD[127].

Coffee consumption had a marginal beneficial association with blood pressure when compared to control in meta-analysis of randomised controlled trials, but failed to reach statistical significance[171]. However, coffee consumption does appear consistently associated with changes to lipid profiles with mean difference in total cholesterol (7.36 mg/dl (95% CI 3.85 to 10.87))[203], LDL-cholesterol (5.44 mg/dl (95% CI 1.38 to 9.51))[203] and triglyceride (12.55 mg/dl (95% CI 3.47 to 21.64))[203] higher in the coffee intervention arms compared to control (1mmol/litre cholesterol ≅ 38.6 mg/dl, 1mmol/litre triglyceride ≅ 88.5 mg/dl[206]). HDL-Cholesterol was lowered in the coffee intervention arms (-0.11 mg/dl (95% CI -0.76 to 0.54)) but this did not reach statistical significance. Increases in cholesterol were mitigated by filtering of coffee, with a marginal rise in cholesterol (mean difference 3.60 mg/dl (95% CI 0.60 to 6.60))[203] and no significant changes to LDL-cholesterol or triglycerides, when compared to unfiltered (boiled) coffee. Similarly decaffeinated coffee appeared to have negligible effect on the lipid profile[203].

A summary of associations between coffee consumption and cardiovascular disease across different categories of exposure is shown in Figure 16.

2.3.3 Cancer

Coffee consumption was associated with lower risk of cancer in a meta-analysis of 40 cohort studies comparing HIGH versus LOW consumption (RR 0.82 (95%CI 0.74 to 0.89))[156], ANY versus NONE (RR 0.87 (95%CI 0.82 to 0.92))[156] and ONE EXTRA CUP/DAY (RR 0.97 (95%CI 0.96 to 0.98))[156]. In a separate article, in non-smokers there was a 2% lower risk of cancer mortality for coffee exposure of ONE EXTRA CUP/DAY (RR 0.98 (95% CI 0.96 to 1.00))[147] and for smokers the risk of cancer mortality increased at all levels of coffee exposure, reaching statistical significance above 4 cups/day, in a non-linear dose-response analysis (no linear dose-response analysis provided).

HIGH versus LOW coffee consumption was associated with lower risk of prostate cancer[141], endometrial cancer[158], melanoma[159], oral cancer[141], leukaemia[156], non-melanoma skin cancer[157] and liver cancer[164]. Statistically significant linear dose-response relationships indicating benefit were also demonstrated for prostate[207], endometrial[141], melanoma[193], and liver cancer[164].

Harmful associations were consistently found for coffee consumption with lung cancer comparing HIGH to LOW consumption (OR 1.56 (95%CI 1.12 to 2.17))[137], ANY versus NONE (RR 1.28 (95% CI 1.12 to 1.47))[168] and ONE EXTRA CUP/DAY (RR1.04 (95% CI 1.03 to 1.05))[168]. However, the effect was diminished in studies that adjusted for smoking and the association was not seen in never-smokers. In the most recent meta-analysis, ANY versus NO coffee consumption in never-smokers was associated with an 8% lower risk of lung cancer (RR 0.92 (95% CI 0.75 to 1.10))[168] and in studies that adjusted for smoking the risk estimate was reduced (RR 1.03 (95% CI 0.95 to 1.12))[168] compared to the overall analysis, and neither reached statistical significance. HIGH versus LOW decaffeinated coffee consumption was shown to be associated with a lower risk of lung cancer in a meta-analysis of two studies[202].

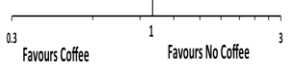
ANY versus NO coffee consumption was associated with higher risk of any urinary tract cancer (OR 1.18 (95% CI 1.01 to 1.38))[169] in a single meta-analysis. However, in other meta-analyses of cohort studies of bladder cancer and renal cancer separately, associations did not reach statistical significance[141].

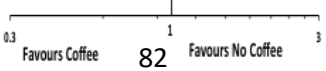
There was no significant association found between coffee consumption and gastric[141,172,186], colorectal[128,141,173], colon[128,173], rectal[128,173], ovarian[141,187], thyroid[149,174], breast[141,156,191], pancreatic[151], oesophageal[141,189], laryngeal cancers[142], lymphoma[141,167], or glioma[152].

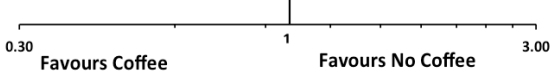
A summary of associations between coffee consumption and cancer across different categories of exposure is shown in Figure 17.

Figure 17: Coffee consumption and cancer outcomes

Outcome	Risk Estimate	Estimate	LCL	UCL	Risk Estimate	Estimate	LCL	UCL	Risk Estimate	Estimate	LCL	UCL
	HIGH vs LOW				ANY vs NONE				1 EXTRA CUP			
Lung Cancer		1.56	1.12	2.17		1.28	1.12	1.47		1.04	1.03	1.05
Lymphoma		1.23	0.75	2.02		1.29	0.92	1.8				
Urinary Tract Cancer						1.18	1.01	1.38				
Laryngeal Cancer		1.22	0.92	1.62								
Bladder Cancer		1.21	0.94	1.55		0.89	0.79	1.01		1.03	0.99	1.06
Gastric Cancer		1.15	0.96	1.37		1.02	0.79	1.31		1.02	0.98	1.07
Ovarian Cancer		1.08	0.91	1.28						1.02	0.99	1.05
Cancer Mortality		1.07	0.98	1.16						1.00	0.99	1.01
Rectal Cancer		1.06	0.95	1.19		0.98	0.85	1.13		1.01	0.99	1.03
Thyroid Cancer		1.00	0.75	1.33		0.89	0.72	1.1				
Breast Cancer		0.99	0.94	1.03		0.95	0.9	1.01		0.99	0.98	1
Pancreatic Cancer		0.99	0.80	1.21						0.99	0.96	1.03
Glioma		0.98	0.79	1.23		0.93	0.76	1.14		1.01	0.96	1.07
Colorectal Cancer		0.96	0.89	1.04		0.83	0.73	0.95		0.99	0.98	1.01
Colon Cancer		0.92	0.83	1.02		0.93	0.81	1.07		0.98	0.97	1.00
All cancer		0.82	0.74	0.89		0.87	0.82	0.92		0.97	0.96	0.98
Prostate Cancer		0.88	0.81	0.96		0.88	0.82	0.95		0.98	0.97	1
Oesophageal Cancer		0.86	0.71	1.04						1.00	0.94	1.06
Non-Melanoma Skin Cancer		0.82	0.74	0.92								
Renal Cancer		0.79	0.54	1.16						0.97	0.75	1.26
Endometrial Cancer		0.76	0.69	0.84		0.86	0.51	1.45		0.94	0.92	0.96
Melanoma		0.76	0.64	0.91						0.97	0.93	1
Oral Cancer		0.69	0.48	0.99								
Leukaemia		0.63	0.41	0.84								
Liver Cancer		0.50	0.43	0.58		0.66	0.55	0.78		0.85	0.81	0.90







2.3.4 Liver and gastrointestinal outcomes

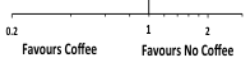
All categories of coffee exposure were associated with lower risk for a range of liver outcomes in addition to liver cancer highlighted in the previous section. ANY versus NO coffee consumption was associated with a 29% lower risk of NAFLD (RR 0.71 (95% CI 0.60 to 0.85))[105], a 27% lower risk for liver fibrosis (OR 0.73 (95% CI 0.56 to 0.94))[65] and an 11% lower risk for liver cirrhosis (OR 0.89 (95%CI 0.73 to 1.08))[65] although the latter did not reach statistical significance. Coffee consumption was also associated with a lower risk of cirrhosis when comparing HIGH versus LOW consumption (OR 0.69 (95%CI 0.44 to 1.07))[160] although again the estimate did not reach statistical significance, and ONE EXTRA CUP/DAY (RR 0.83 (95%CI 0.78 to 0.88))[198]. ONE EXTRA CUP/DAY exposure was also significantly associated with a lower risk of cirrhosis mortality (RR 0.74 (95% CI 0.59 to 0.86))[198]. In a single article[208], for meta-analyses of coffee consumption and chronic liver disease, HIGH versus LOW (RR 0.35 (95%CI 0.22 to 0.56)), ANY versus NONE (RR 0.62 (95%CI 0.47 to 0.82)), and ONE EXTRA CUP/DAY (RR 0.74 (95%CI 0.65 to 0.83)) were all beneficially associated.

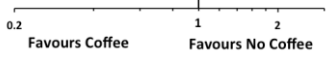
Coffee consumption was also consistently associated with lower risk of gallstone disease[133] and in a non-linear dose response analysis risk sequentially reduced as consumption increased from 2 to 6 cups/day[133]. Comparing HIGH versus LOW coffee consumption there was a marginally higher risk of gastro-oesophageal reflux disease but this did not reach statistical significance[148].

A summary of associations between coffee consumption and liver and gastro-intestinal outcomes across different categories of exposure is shown in Figure 18.

Figure 18: Coffee consumption and liver and gastrointestinal outcomes

Outcome	Risk Estimate	Estimate	LCL	UCL	Risk Estimate	Estimate	LCL	UCL	Risk Estimate	Estimate	LCL	UCL
	HIGH vs LOW				ANY vs NONE				1 EXTRA CUP			
Gastrointestinal Reflux		1.06	0.94	1.19								
Gallstones		0.83	0.76	0.89						0.95	0.91	1.00
Liver Fibrosis						0.73	0.56	0.94				
NAFLD						0.71	0.6	0.85				
Cirrhosis		0.69	0.44	1.07		0.89	0.73	1.08		0.77	0.64	0.87
Chronic Liver Disease		0.35	0.22	0.56		0.62	0.47	0.82		0.74	0.65	0.83





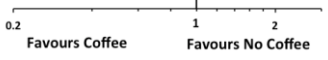
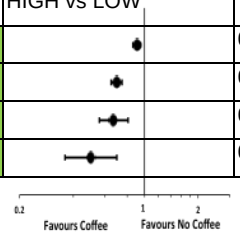
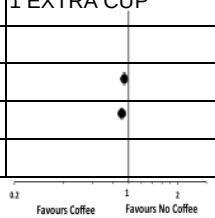


Figure 19: Coffee consumption and metabolic outcomes

Outcome	Risk Estimate	Estimate	LCL	UCL	Risk Estimate	Estimate	LCL	UCL	Risk Estimate	Estimate	LCL	UCL
	HIGH vs LOW				ANY vs NONE				1 EXTRA CUP			
Metabolic Syndrome		0.91	0.86	0.95								
Type II diabetes		0.7	0.65	0.75						0.94	0.93	0.95
Renal Stones		0.67	0.56	0.81						0.91	0.88	0.95
Gout		0.5	0.36	0.7								





2.3.5 Metabolic outcomes

Coffee consumption was associated with lower risk of T2DM and this was consistent across exposure classification. HIGH versus LOW coffee consumption was associated with a 30% reduced risk of T2DM (RR 0.70 (95%CI 0.65 to 0.75))[129] and 6% reduction for each ONE EXTRA CUP/DAY (RR 0.94 (95%CI 0.93 to 0.95))[195]. The risk of T2DM was lower for each dose of ascending consumption between 1 and 6 cups where a non-linear dose response analysis was conducted.[129] Decaffeinated coffee consumption also appears to have similar beneficial associations with T2DM and of comparable magnitude[129].

For metabolic syndrome HIGH versus LOW coffee consumption was associated with 9% lower risk (RR 0.91 (95%CI 0.86 to 0.95))[134]. HIGH versus LOW consumption was also found to be statistically significantly associated with a lower risk of renal stones[161] and gout[163].

A summary of associations between coffee consumption and metabolic outcomes across different categories of exposure is shown in Figure 19.

2.3.6 Renal Outcomes

There was a lower risk of urinary incontinence[179] and chronic kidney disease[181] when comparing coffee consumption of ANY versus NONE but neither association reached statistical significance, and the meta-analyses included cross-sectional studies.

A summary of associations between coffee consumption and renal outcomes across different categories of exposure is shown in Figure 20.

Figure 20: Coffee consumption and renal outcomes

Outcome	Risk Estimate	Estimate	LCL	UCL	Risk Estimate	Estimate	LCL	UCL	Risk Estimate	Estimate	LCL	UCL
	HIGH vs LOW				ANY vs NONE				1 EXTRA CUP			
Urinary Incontinence						0.75	0.54	1.04				
Chronic Kidney Disease						0.71	0.47	1.08				

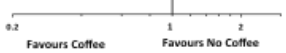
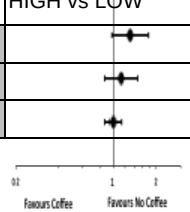
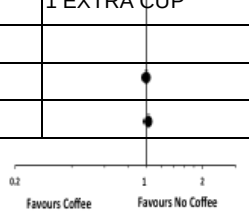


Figure 21: Coffee consumption and musculoskeletal outcomes

Outcome	Risk Estimate	Estimate	LCL	UCL	Risk Estimate	Estimate	LCL	UCL	Risk Estimate	Estimate	LCL	UCL
	HIGH vs LOW				ANY vs NONE				1 EXTRA CUP			
Rheumatoid Arthritis		1.31	0.97	1.77								
Hip Fracture		1.13	0.86	1.48						1.00	0.96	1.03
Fracture		0.99	0.86	1.14						1.03	1	1.06





2.3.7 Musculoskeletal outcomes

There is inconsistency in the evidence of association of coffee consumption and musculoskeletal outcomes. There were no statistically significant overall associations between HIGH versus LOW or ONE EXTRA CUP/DAY coffee consumption and fracture[150,185], or hip fracture risk[145,190]. However, the effects appear to be modified by gender. In a subgroup analysis, HIGH versus LOW consumption was associated with an increased risk of fracture in women (RR 1.14 (95% CI 1.05 to 1.24) whilst a decreased risk in men (RR 0.76 (95% CI 0.62 to 0.94))[150](test of interaction (ratio of relative risks (women:men) = 1.50 (95% CI 1.20 to 1.88), p<0.001).

An association between HIGH versus LOW coffee consumption and hip fracture risk was also seen in a subgroup analysis of women (RR 1.27 (95% CI 0.94 to 1.72)[145] but not men (RR 0.53 (95% CI 0.38 to 1.00)[145] but the estimates did not reach statistical significance (test of interaction (ratio of relative risks (women:men) = 2.40 (95% CI 1.35 to 4.24), p<0.01).

For consumption of ONE EXTRA CUP/DAY there was also an association with increased risk of fracture in women (RR 1.05 (95% CI 1.02 to 1.07))[185] but lower risk in men (RR 0.91 (95% CI 0.87 to 0.95))[185] (test of interaction (ratio of relative risks (women:men) = 1.15 (95% CI 1.10 to 1.21), p<0.001).

Taken together, these results suggest that gender may be a significant effect modifier in the association between coffee drinking and fracture risk. Total and decaffeinated coffee consumption were also associated with a higher risk of rheumatoid arthritis[138,139] but neither reached statistical significance.

A summary of associations between coffee consumption and musculoskeletal outcomes across different categories of exposure is shown in Figure 21.

2.3.8 Neurological outcomes

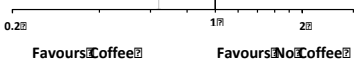
Coffee consumption was associated with a lower risk of Parkinson's disease, even after adjusting for smoking, and was consistent across all categories of exposure[130,182,197]. Decaffeinated coffee was also associated with a lower risk of Parkinson's disease but did not reach statistical significance[130]. In meta-analyses of cohort studies, coffee

consumption had a consistent association with lower risk of depression[196,209] and cognitive disorders, especially for Alzheimer's Disease (RR 0.73 (95% CI 0.55 to 0.97))[153].

A summary of associations between coffee consumption and neurological outcomes across different categories of exposure is shown in Figure 22.

Figure 22: Coffee consumption and neurological outcomes

Outcome	Risk Estimate	Estimate	LCL	UCL	Risk Estimate	Estimate	LCL	UCL	Risk Estimate	Estimate	LCL	UCL
	HIGH vs LOW				ANY vs NONE				1 EXTRA CUP			
Cognitive Decline		0.97	0.85	1.11						1.00	0.98	1.02
Depression		0.88	0.79	0.99						0.92	0.87	0.97
Alzheimer's Disease		0.73	0.55	0.97		0.73	0.54	0.99		1.02	0.95	1.08
Parkinson's Disease		0.64	0.53	0.76		0.64	0.53	0.77		0.88	0.77	1.00



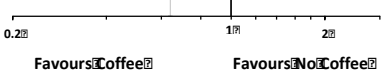
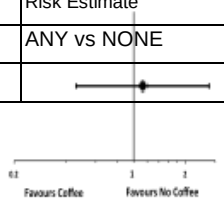


Figure 23: Coffee consumption and gynaecological outcomes

Outcome	Risk Estimate	Estimate	LCL	UCL	Risk Estimate	Estimate	LCL	UCL	Risk Estimate	Estimate	LCL	UCL
	HIGH vs LOW				ANY vs NONE				1 EXTRA CUP			
Endometriosis						1.13	0.46	2.76				



2.3.9 Gynaecological outcomes

ANY versus NO coffee consumption was associated with a higher risk of endometriosis but did not reach statistical significance[170].

A summary of associations between coffee consumption and gynaecological outcomes across different categories of exposure is shown in Figure 23.

2.3.10 Antenatal Coffee Exposure

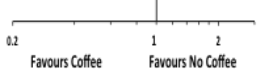
Coffee consumption appears to be consistently associated with harm in different pregnancy-related outcomes. HIGH versus LOW coffee consumption was associated with higher risk of low birth weight (OR 1.31 (95%CI 1.03 to 1.67))[140], pregnancy loss (OR 1.46 (95%CI 1.06 to 1.99))[131], 1st trimester preterm birth (OR 1.22 (95%CI 1.00 to 1.49))[143] and 2nd trimester preterm birth (OR 1.12 (95%CI 1.02 to 1.22))[143]. However no statistically significant association was found for any category of coffee consumption and 3rd trimester preterm birth[143], neural tube defects[177], and congenital malformations of the oral cleft[144] or cardiovascular system[144]. A Cochrane meta-analysis of a single randomised-controlled trial investigating coffee caffeine consumption on birth weight, pre-term birth and small for gestational age, suggested none of the outcomes reached statistical significance[204].

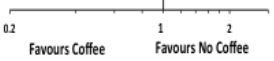
Coffee consumption in pregnancy is also associated with higher risk of childhood leukaemia including HIGH versus LOW (OR 1.57 (95%CI 1.16 to 2.11))[136] and ANY versus NONE (OR 1.44 (95% CI 1.07 to 1.92))[165,166].

A summary of associations between coffee consumption and antenatal-related outcomes across different categories of exposure is shown in Figure 24.

Figure 24: Coffee consumption and antenatal-related outcomes

Outcome	Risk Estimate	Estimate	LCL	UCL	Risk Estimate	Estimate	LCL	UCL	Risk Estimate	Estimate	LCL	UCL
	HIGH vs LOW				ANY vs NONE				1 EXTRA CUP			
Acute Childhood Leukaemia		1.57	1.16	2.11		1.44	1.07	1.92				
Pregnancy Loss		1.46	1.06	1.99						1.04	1.03	1.05
Low Birth Weight		1.31	1.03	1.67						1.16	0.91	1.48
1st Trimester Preterm Birth		1.22	1	1.49								
3rd Trimester Preterm Birth		1.22	0.95	1.57								
Oral Cleft Malformations		1.21	0.92	1.59								
Cardiovascular Malformations		1.16	0.9	1.5								
2nd Trimester Preterm Birth		1.12	1.02	1.22								
Neural Tube Defects						0.86	0.51	1.45				





2.3.11 Heterogeneity of included studies

We reanalysed 83% of comparisons for HIGH versus LOW, and 79% for ANY versus NONE. None of the linear dose-response analyses were reanalysed. Approximately 40% of the 83 meta-analyses that we reanalysed had a statistically significant heterogeneity and 90% of these had an I^2 >50%. Studies included in each meta-analysis varied by many factors including the geography and ethnicity of the population of interest, the type of coffee consumed, the method of coffee consumption ascertainment and the coffee exposure measure, duration of follow-up and outcome assessment. For the 54 that we were unable to reanalyse, only four used a fixed effects model, 19% had significant heterogeneity, and 27% of meta-analyses did not publish heterogeneity.

2.3.12 Publication bias of included studies

We performed Egger's regression test in 40% of the meta-analyses in our reanalysis and 20% of these had statistical evidence of publication bias. This included HIGH versus LOW comparisons for type II diabetes[129] (p=0.049), stroke[127] (p=0.09) gastro-oesophageal reflux disease[148] (p=0.04), bladder cancer[141] (p<0.01), endometrial cancer[158] (p=0.03), and hip fracture[145] (p=0.02), and in the meta-analysis of randomised controlled trials for total cholesterol (p<0.01). The remaining 60% contained insufficient number of studies to use Egger's regression test.

For meta-analyses that we were unable to re-analyse, none reported significant publication bias or did not provide information. It is possible that unmeasured publication bias exists in many of the summary estimates we have presented and not assessed.

2.3.13 AMSTAR and GRADE classification of included studies

The AMSTAR (*methodological quality*) score achieved across all studies was a median of 5 out of 11 (range 2 to 9, interquartile range 5 to 7). Eleven studies were downgraded due to using a fixed, rather than random effects, model. A breakdown of AMSTAR scores for studies representing each outcome is shown in appendix A. Using GRADE classification for *quality of evidence*, approximately 25% of articles were rated as being of 'low' and 75% as 'very low' quality. Due to risk of bias, inconsistency or imprecision, even the meta-analyses of randomised controlled trials were graded as low quality of evidence. Quality of evidence was only increased in outcomes identified as having a significant dose-response

effect, or large magnitude of effect, without significant other biases. A breakdown of GRADE scores for studies representing each outcome is shown in appendix B.

2.4 Discussion

2.4.1 Principal findings and possible explanations

Coffee consumption is more often associated with benefit than harm across a range of health outcomes and different coffee exposure categories including HIGH versus LOW, ANY versus NONE, and ONE EXTRA CUP/DAY. Exposure to coffee has been the subject of numerous meta-analyses on a diverse range of health outcomes and the umbrella review was conducted to draw this existing evidence together. A total of 201 meta-analyses of observational research with 67 unique outcomes and 17 meta-analyses of randomised-controlled trials with 9 unique outcomes were identified and included in the review.

Coffee consumption was associated with lower risk of all-cause mortality[147], cardiovascular mortality[147] and total cancer[156] and specific cancers including prostate cancer[141,176,207], endometrial cancer[141,158,178], melanoma[193,210], non-melanoma skin cancer[157] and liver cancer[100]. Coffee consumption was also associated with lower risk of metabolic conditions including T2DM[129,195], metabolic syndrome[134], gallstones[133], gout[163], renal stones[161] and liver conditions including hepatic fibrosis[65], cirrhosis[65,198] cirrhosis mortality[198], and chronic liver disease combined[208]. Liver conditions standout as consistently having the highest magnitude of apparent benefit compared with other outcomes across exposure categories. Finally, there appears to be beneficial associations between coffee consumption and risk of Parkinson's disease[130,182,197], depression[196,209] and Alzheimer's disease[153].

Harmful associations between coffee consumption and health outcomes were rare except for those related to pregnancy, and for fracture risk in women. After adjusting for smoking, coffee consumption in pregnancy appears to be associated with harmful outcomes related to low birth weight[140], preterm birth[143], and pregnancy loss[131]. These pregnancy associations were subgroup analyses from articles investigating total caffeine exposure, which showed similar associations, and from a single meta-analysis for each outcome. Harmful associations were also found between coffee consumption and congenital malformations although these did not reach statistical significance[144]. There is biological

plausibility backing these harmful associations. The half-life of caffeine is known to double during pregnancy[211] and therefore the relative dose of caffeine from equivalent per cup consumption will be much higher compared to when not pregnant. Caffeine also passes easily across the placenta[212] where foetal activity of the caffeine metabolising enzyme, CYP1A2, is low, resulting in prolonged foetal exposure to caffeine[213]. No significant associations were identified between coffee exposure and neural tube defects[177]. However, for this outcome, most studies were of case-control design, and therefore prone to recall bias. Maternal coffee exposure also has harmful associations with acute leukaemia of childhood[136,165,166]. Evidence for this also comes from case-control studies.

There appears to be effect modification by gender for the association of coffee consumption and fracture risk. The most recent meta-analyses found a 14% increased risk of fracture when comparing HIGH versus LOW consumption[150] and 5% increased risk of fracture for ONE EXTRA CUP/DAY consumption[185] in women. Conversely, in men, coffee consumption was beneficially associated with lower risk of fracture. Caffeine is the component of coffee that has been linked to the increased fracture risk in women, with potential influence on calcium absorption[214] and bone mineral density[215]. However, a recent comprehensive systematic review of the health effects of caffeine concluded that a caffeine intake of 400mg/day (approximately 4 cups of coffee) was not associated with adverse effects on risk of fracture, falls, bone mineral density or calcium metabolism[216]. There is more limited evidence to draw conclusions at higher caffeine intakes. Notably, many of the studies included in the meta-analyses of coffee consumption and fracture risk did not adjust for important confounders such as BMI, alcohol, smoking, or intakes of calcium and vitamin D. Caffeine consumption may only be associated with a lower risk of low bone mineral density in women with inadequate calcium intake[217], and small amounts of milk may be needed to offset any negative effects on calcium absorption[214]. The type of coffee consumed may therefore be an important factor. Coffee and caffeine have also been linked with effects on oestrogen metabolism in pre-menopausal women[218] and increased levels of sex hormone binding globulin (SHBG) in observational research of post-menopausal women[219]. Low levels of oestradiol and high SHBG are known to be associated with fracture risk[220,221]. The effect of coffee consumption on SHBG has not been demonstrated in small-scale randomised controlled trials[222]. There is consistent evidence suggesting coffee consumption is associated with a lower risk of endometrial cancer[158], but no clear evidence for associations with ovarian cancer[141,187], and beneficial associations with oestrogen-receptor negative breast cancer[191]. The effect of coffee consumption on fracture risk in women may therefore vary depending on levels of

endogenous sex hormones, dietary calcium[217] and effects of other known risk factors for osteoporosis[223].

Where meta-analyses have suggested harmful associations between coffee consumption and lung cancer, this can largely be explained by inadequate adjustment for smoking. Smoking is known to be associated with higher coffee consumption[224] and harmfully with many health outcomes and may therefore act as both a confounder and effect modifier. Galarraga and Boffetta addressed the possible confounding by smoking in a recent meta-analysis[168] of coffee consumption and lung cancer risk by performing the meta-analysis in never-smokers and no harmful association was detected. They then performed the meta-analysis in only those studies that adjusted for smoking and the magnitude of the apparent harmful association was reduced and was no longer statistically significant. It is likely that residual confounding by smoking can explain this apparent harmful association.

For randomised controlled trials, evidence is more limited. Coffee has only been given as an intervention for short durations and limited to a small number of outcomes, including blood pressure, lipid profiles and one trial in pregnancy. There does appear to be consistent evidence for small changes in the lipid profile with increases in total cholesterol, LDL-cholesterol and triglyceride and this is believed to be due to the action of diterpenes[225]. The method of preparation is an important factor since instant and filtered coffee contain negligible amounts of diterpenes compared to espresso, boiled and cafetière coffee[225]. In the meta-analysis presented in our review, the effect of filtered coffee consumption on lipids was negligible. Studies have also suggested that the dose of diterpenes needed to cause hypercholesterolaemia is likely to be much higher than the dose needed for beneficial anti-carcinogenic effects[27] that have been associated with these compounds. Coffee consumption does not appear to be associated with adverse cardiovascular outcomes, including mortality after myocardial infarction[162] and this is reassuring such that the clinical relevance of such small increases in total cholesterol, LDL-cholesterol and triglyceride due to unfiltered coffee are doubtful. The coffee associated changes in the lipid profile have also been shown to reverse with abstinence[226].

Intakes of 3-4 cups per day have been shown to be associated with the largest relative risk reduction in all-cause mortality, cardiovascular disease mortality, cardiovascular disease, and heart failure, where evidence for a non-linear dose response relationship has been shown. Importantly, increasing consumption beyond this intake does not appear to be associated with increased risk of harm, but benefit is reduced. In T2DM, despite statistically significant non-linearity, relative risk reduced sequentially from 1 through to 6

cups/day. Imprecision observed for some outcomes at higher levels of consumption may be due to smaller numbers of participants consuming coffee at these levels.

There are plausible biological mechanisms for coffee benefitting liver health as described in chapter 1 and the umbrella review showed that coffee consumption consistently had the largest magnitude of beneficial effect for liver outcomes compared to others. For other outcomes biological plausibility seems linked to antioxidant, anti-inflammatory and anti-carcinogenic effects. Coffee has been shown to contribute more daily dietary antioxidant intake than tea, fruit, and vegetables[227]. Chlorogenic acid is the most abundant antioxidant in coffee and alternative antioxidant organic compounds are formed during the roasting process[228]. Caffeine itself is also a significant antioxidant. The diterpenes, cafestol and kahweol, are thought to have an anti-carcinogenic effect by inducing enzymes involved in carcinogen detoxification and stimulation of intracellular antioxidant defence[27].

Decaffeinated coffee is compositionally similar to caffeinated coffee apart from having little or no caffeine[229], but similar amounts of chlorogenic acids and diterpenes. In our umbrella review we identified a total of 16 unique outcomes for associations with decaffeinated coffee but most studies did not provide data on decaffeinated coffee consumption. Largest relative risk reduction was seen at intakes of 2-4 cups/day decaffeinated coffee for all-cause and cardiovascular mortality in a non-linear dose-response and of similar magnitude to caffeinated coffee. Marginal benefit in the association between decaffeinated coffee and cancer mortality did not reach statistical significance. The associations between HIGH versus LOW decaffeinated coffee consumption and lower risk of T2DM[129] and endometrial cancer[158] were of a similar magnitude to total or caffeinated coffee, and there was a small beneficial association between decaffeinated coffee consumption and lung cancer[202]. Decaffeinated coffee consumption would have much lower power to detect an effect due to the smaller number of participants drinking decaffeinated coffee and the other outcomes investigated showed no statistically significant associations. Importantly, there were no convincing harmful associations identified between decaffeinated coffee consumption and health outcomes. Most coffee assessment tools do not adequately account for people who may have switched from caffeinated to decaffeinated consumption[117] and decaffeinated coffee drinkers may be different from caffeinated coffee drinkers including age, co-morbidities and other lifestyle factors.

2.4.2 Strengths and weaknesses and in relation to other studies

The umbrella review systematically summarised the current evidence for coffee consumption exposure and any health outcome for which a previous meta-analysis had been conducted. A systematic methodology was used that included a robust search strategy using four scientific literature databases. Two investigators independently selected studies and extracted data. Each meta-analysis was repeated using a standardised approach that included the use of random effects analysis and produced measures of heterogeneity and publication bias to allow better comparison across outcomes. However, this was not possible for all meta-analyses due to limited data published in each article, and original primary studies were not accessed. Standard approaches were used to assess methodological quality (AMSTAR) and quality of the evidence (GRADE).

AMSTAR has good evidence of validity and reliability[120] and assisted us in identifying the highest quality of evidence for each outcome. However, AMSTAR has limitations such as allowing only a one-point loss for a poor analysis technique, so would not capture multiple issues within an individual meta-analysis methodology. Additionally, whilst scoring a point for performing a quality assessment of the original articles it is unable to account for the actual quality of these.

One recurring issue for many meta-analyses was the use of pooling a combination of odds ratio (OR), relative rates and hazard ratios (HR), in order that they could combine studies with different measures and produce a relative risk (RR). Statistically, this is acceptable when the outcome is uncommon such that the odds ratio will be similar to the relative risk[230], but the OR will always be more extreme[230]. For rare events, relative rates and hazard ratios are similar to the RR when censoring is uncommon or evenly distributed between exposed and unexposed groups[230]. It was not possible to make a judgement on suitability of pooling due to insufficient information in most of the articles. Only one meta-analysis produced a summary statistic using hazard ratios[187]. We did not downgrade the AMSTAR score where this assumption had been made, and we did not downgrade meta-analyses for failing to consider uncertainty in variance estimates since this was universally unstated[231]. Reassuringly, the majority of dose-response meta-analyses included in the umbrella review and selected as the highest form of evidence for each outcome accounted for lack of independence in comparison (same unexposed group) by using the methods proposed by Greenland and Longnecker[232]

Studies included in the umbrella review were mainly meta-analyses of observational studies. A strength of the umbrella review was inclusion of only cohort studies, or subgroup analyses of cohort studies where available. In meta-analyses that we were unable to re-analyse and where subgroup analysis did not allow the disentanglement of study design, the presented results were from the combined estimates of all included studies. Despite this, observational research is low quality in the hierarchy of evidence and using GRADE classification most outcomes are recognised as having 'very low', or 'low' quality of evidence where a dose-response relationship exists. Large effect sizes of >2 or <0.5 can permit observational evidence to be upgraded in GRADE and only the association between HIGH versus LOW coffee consumption and both liver cancer[100] and chronic liver disease[100] reached this magnitude with estimates of 0.50 and 0.35 respectively for HIGH versus LOW coffee exposure. Coffee consumption associations with liver outcomes consistently had larger effect sizes compared to other outcomes across exposure categories. Our reanalysis did not change our GRADE classification for any outcome.

A limitation of the umbrella review was that we did not reanalyse any of the dose-response meta-analyses since the data needed to compute these were not generally available in the meta-analysis articles and we did not review the primary studies that would have facilitated this. It was decided that reanalysing the dose-response data was unlikely to result in changes to the GRADE classification. In our reanalysis of the comparison of HIGH versus LOW and ANY versus NONE, we used data available in the published meta-analyses articles and therefore assumed the exposure and estimate data for component studies had been published accurately which may not have been the case.

We were able to produce estimates for publication bias using Egger's test for meta-analyses containing 10 or more studies[124] but were unable to conduct alternative tests, such as Peters' test[233], which is more appropriate for binary outcomes. Peters' test needs cases and non-cases for each level of exposure and this detail was largely unavailable in the meta-analyses articles. We did not calculate excess significance tests which attempt to compare the number of studies that have statistically significant results with the number expected, based on the sum of the statistical powers from individual studies, and using an effect size equal to the largest study in the meta-analysis[234], in order to detect reporting bias. However, these tests have not been fully evaluated and therefore they are not currently recommended as an alternative to traditional tests of publication bias[235].

Further bias in methodology may have occurred due to the same author conducting multiple meta-analyses for different health outcomes and using the same cohort. Whilst

statistically independent, any bias in methodology of design or conduct of the original cohorts may filter through the totality of evidence.

Two large cohort studies published recently are in agreement with the beneficial association between coffee consumption and all-cause mortality highlighted in our umbrella review. The first was a large cohort study that included 10 European countries, and 521,330 participants followed for a mean period of 16 years during which there were 41,693 deaths[236]. Compared to no coffee consumption, the highest quartile of coffee consumption was associated with a 12% lower risk of all-cause mortality in men (HR 0.88 (95% CI 0.82 to 0.95)), and a 7% lower risk in women (HR 0.93 (95% CI 0.87 to 0.98)). There were also beneficial associations between coffee drinking and a range of cause-specific mortality including digestive tract disease mortality in men and women, and circulatory and cerebrovascular disease mortality in women. Adjustments were made for a large number of potential confounding factors including education, lifestyle (smoking, alcohol, physical activity), dietary factors and body mass index. The only harmful association identified was between coffee consumption and an increased risk of ovarian cancer mortality, when comparing the highest quartile of consumption to no coffee (HR 1.31 (95%CI 1.07 to 1.61)). No prevailing hypothesis was presented. In our umbrella review, HIGH versus LOW and ONE EXTRA CUP/DAY coffee consumption was associated with an 8% and 2% increased risk of incident ovarian cancer respectively, but neither reached statistical significance.

In the second study, a North American cohort was followed up for 16 years and included 185,855 participants of which 58,397 died[237]. Coffee consumption of ≥4 cups per day was associated with an 18% lower risk of mortality (HR 0.82 (95% CI 0.78 to 0.87)) after adjustment for smoking and other factors. The findings were consistent by gender and ethnicity. Beneficial associations were also seen between coffee consumption and mortality from heart disease, cancer, chronic lower respiratory disease, stroke, diabetes and kidney disease. Importantly, no harmful associations were identified although subtypes of cancer mortality were not published.

Residual confounding may explain some of the associations between coffee consumption and health outcomes. Smoking, age, BMI, and alcohol consumption are all associated with both coffee consumption and a considerable number of health outcomes. These relationships may differ in magnitude and even direction between populations. Residual confounding by smoking could make a beneficial association less pronounced or increase a harmful one where smoking is also associated with an outcome. Other confounding factors may include higher income or education which benefit health and may afford

greater access to coffee drinking. Randomised controlled trials can distribute known or unknown confounders randomly between intervention and control groups and this highlights the importance of this approach to better understand cause and effect. However, for many outcomes a randomised controlled trial would be challenging. Another approach to mitigate effects of confounding factors is Mendelian Randomisation (MR). MR studies can also help to reduce the effects of confounding due to random distribution of confounders between genotypes of known function related to the outcome of interest. MR has been used to investigate the association between coffee consumption and lower risk of T2DM[238] and all-cause, and cardiovascular mortality[239], and these concluded that there was no genetic evidence for a causal relationship. However, the authors point out that the MR approach relies on the assumption of linearity between all categories of coffee intake and may not capture non-linear differences. Genetic variability in coffee and caffeine metabolism may influence the magnitude, frequency and duration of exposure to caffeine and other coffee bioactive compounds. The risk of hypertension associated with coffee was found to vary depending on the CYP1A2 genotype[240]. Those with alleles for slow caffeine metabolism were at increased risk of hypertension compared to those with alleles for fast caffeine metabolism suggesting a genetic modification of risk.

Bias from reverse causality can also occur in observational studies. In case-control studies, symptoms from disease may have had a direct effect on coffee consumption or changes to consumption may stem from a belief about whether it was healthy or not. Meta-analyses of cohort studies or cohort subgroup analyses were included in the present review since they are less prone to this type of bias. However, even prospective cohort studies can be affected by reverse causality if apparently healthy participants at recruitment have reduced their coffee intake due to early symptoms of a disease.

Most meta-analyses produced summary effects from individual studies that measured coffee exposure by number of cups/day. However, some individual studies used number of times/day, servings/day, occasions/day, millilitres/day, cups/week, times/week, cups/month and drinkers versus non-drinkers to measure coffee consumption, suggesting that misclassification in exposure was likely. There is no universal standard cup size and the bioactive components of coffee in a single cup will vary depending on the type of bean (e.g. Arabica versus Robusta), degree of roasting and preparation method, quantity of bean, grind setting and brew type used. Therefore, studies that are comparing coffee consumption by cup measures may be comparing a range of coffee exposure. Furthermore, the range of number of cups/day classified as both HIGH and LOW consumption from different individual studies varied substantially for inclusion in each meta-analysis and this was the most frequently used exposure measure. However,

consistent results across meta-analyses and exposure categories suggest that a cup/day measure produces a reasonable differential in exposure. Additionally, any misclassification in exposure is likely to be non-differential and would more likely dilute any risk estimate rather than strengthen it, pushing it towards the null. This is further discussed in chapter 3.

We excluded systematic reviews without meta-analyses but only respiratory outcomes[241] and sleep disturbance[242] had systematic review without performing a meta-analysis. There may be important well-conducted studies that have assessed coffee consumption in relation to outcomes for which no systematic review or meta-analysis have been conducted to date. Additionally, our focus was on defined health outcomes rather than physiological effects of coffee such as increased heart rate, central nervous system stimulation and feelings of anxiety that have not been captured in this review. These effects should be considered in individuals taking medications which may have similar physiological effects or in those trying to avert anxiety.

Despite our broad inclusion criteria, only one meta-analysis was identified that focused on a population of people with established disease, with most investigating associations in general population cohorts. This was a meta-analysis of two small cohort studies investigating mortality risk in people who had experienced a myocardial infarction[162]. Our summation of the existing body of evidence should therefore be viewed in this context and suggests that the association of coffee consumption in modifying the natural history of established disease remains unclear.

2.5 Conclusions and recommendations

This umbrella review has systematically assimilated this vast amount of existing evidence between coffee consumption and multiple health outcomes where it has been published in a meta-analysis. Most of this evidence is only ‘low’ or ‘very low’ quality based on the predominance of observational study design and associated biases. Beneficial associations between coffee consumption and liver outcomes (fibrosis, cirrhosis, chronic liver disease, and liver cancer) have relatively large and consistent effect sizes compared to other outcomes. However, coffee consumption is also beneficially associated with a range of other health outcomes and importantly does not appear to have definitive harmful associations with any outcomes aside from pregnancy. The association of coffee consumption with fracture risk in women remains uncertain and warrants further investigation. Residual confounding may explain some of the observed associations and

MR studies could be applied to a range of outcomes, including fracture risk, to help address this issue. More definitive conclusions may come from randomised controlled trials which would only be practical using valid proxies of significant patient outcomes, and could be especially useful in relation to coffee consumption and chronic liver disease where a number of valid proxies for disease severity exist. This is further discussed in the final chapter. Reassuringly, our analysis indicates that future randomised controlled trials where the intervention is increasing coffee consumption, possibly optimised at 3-4 cups of coffee per day, would be unlikely to result in significant harm to participants. However, pregnancy, or risk of pregnancy, and women with risk factors for higher fracture risk, would be justified exclusion criteria for participation in a coffee treatment study.

Chapter 3: Misclassification of coffee consumption data and the development of a standardised coffee unit measure

3.1 Background

3.1.1 Classification of different preparation methods

There are numerous methods for preparing a cup of coffee. All have the goal of converting coffee beans into palatable beverages by essentially mixing the ground coffee bean, or a concentrated and dried soluble version, with water. Methods to apply water to freshly ground coffee can be simplified into four main processes - filtration, boiling, application of pressure, and steeping.[19]

3.1.1.1 Filter coffee

Filtration is the process by which hot water is poured over coffee grounds above a filter. The filter is typically made out of paper, but could be any material. The ground coffee soaks up the water and soluble compounds within the coffee dissolve and the liquid passes through the filter into a vessel below. More recently there has been an increase in popularity of 'pour-over' coffee, which is a manual method for applying the water onto the coffee, but automatic filter coffee machines have been popular for many years. Filter coffee is popular in Northern European countries and North America. One key difference between filter coffee and other methods is the lower concentration of diterpenes because they do not readily pass through the filter paper.

3.1.1.2 Boiled coffee

Boiled coffee is conceptually the simplest method to prepare coffee and simply is the boiling of very finely coffee grounds in a suitable vessel. It would have been one of the earliest methods of creating coffee and remains a popular method in Turkey, Russia, Greece, Africa and the Middle East. A hybrid method between filtration and boiling coffee is percolation in which boiled water is repeatedly passed through a chamber containing coffee. Coffee percolaters were popular in the 1960's and have largely been replaced by filter machines.

3.1.1.3 Pressurised coffee

Espresso machines allow pressurised water to pass through a sealed unit containing finely ground coffee grounds and the application of pressure allows a greater degree of coffee oil to be extracted. The resultant ‘shot’ of coffee tends to be more concentrated and aromatic compared to other preparation methods and contains a higher concentration of caffeine and chlorogenic acids. Espresso ‘shots’ can be consumed directly or have milk added in a number of different combinations to create drinks such as cappuccinos, lattes, flat whites, and Americanos. Stove top Moka pots, otherwise known as Macchinettas, are also devices that utilise pressure from steam to force water through a basket of tightly packed coffee and into a holding chamber.

3.1.1.4 Steeped coffee

The cafetière or French Press is a device for making coffee using the steeping method. Ground coffee is added to a cylindrical container, typically constructed from glass, and hot water is poured over the top and left to steep for several minutes. During steeping, soluble compounds within the coffee are dissolved. A meshed plunger is then inserted into the cylinder and pushed down to press the grounds to the bottom of the cylinder leaving the liquid portion above to be poured out.

An Aeropress is a device for making coffee that utilises a combination of filter, steeping and pressure. It resembles a large syringe to which manual pressure is applied to pass steeped coffee through a filter paper into a cup positioned underneath.

Siphon coffee machines are another type of steeping method where heated water passes through a glass tube to mix with coffee in a reservoir and then allowed to cool. During cooling a vacuum is created in the original vessels and this pulls the now coffee mixture back down the tube. Siphon coffee makers were popular at the end of the 19th Century but have also enjoyed a recent surge in popularity.

3.1.1.5 Instant coffee

Instant coffee remains the most popular coffee preparation method in the UK. As the name suggests, instant coffee can be prepared very quickly, by simply pouring recently boiled water into cup or mug containing a quantity of the dried instant coffee powder or granules that are fully soluble. Instant coffee is created by freeze-drying or spray-drying liquid coffee that has already been brewed by a process similar to percolation.

3.1.2 Limitations of existing research on coffee and health

There are several limitations to the current evidence between coffee and health, linked to the fact that most evidence originates from observational studies. There is risk that the apparent relationship between an exposure and an outcome deviates from the true relationship as a result of chance, bias or confounding.

Chance, or random error, can never be completely eliminated. Researchers can reduce the risk of type I errors (falsely rejecting the null hypothesis) through careful design, pre-specifying outcomes, and taking into account multiple outcomes in the analysis. Researchers can reduce the risk of type II errors (falsely retaining the null hypothesis) by powering studies appropriately.

Observational coffee research is at risk from confounding because other factors may be associated with both coffee drinking and the outcome of interest, and falsely lead to apparent beneficial or harmful associations unless this other factor is taken into account by stratification or adjustment in the analysis. Unknown confounding factors cannot be accounted for in such study designs. Even when adjustments are made, residual confounding from known confounding factors can still cause spurious results. A good example of a confounding factor in coffee research is that of smoking as highlighted in chapter 2. Smoking confounds an apparent harmful association between coffee drinking and both gastric and lung cancer. On average, people who smoke drink more cups a day of coffee than people who do not smoke[224]. This consistent association also has biological plausibility because smoking induces the activity of cytochrome P450 enzymes in the liver and the metabolism of caffeine is increased. This increase in metabolism reduces the apparent effects of caffeine and people who smoke would be able to drink more caffeinated coffee before experiencing any feelings of sufficiency. Likewise, it is well established that smoking is a causative factor in many cancers including gastric and lung

cancer. Where studies have stratified by smoking status or adjusted for smoking in the analysis, the apparent harmful associations have been reduced, reversed or lost statistical significance[168,243]. Similarly, there may be apparent beneficial associations that are confounded by beneficial lifestyle or social factors that encourage both coffee drinking and health such as income and education.

To circumvent the issue of confounding that prevents firm causative conclusions between coffee drinking and health outcomes, other study designs can be used. This includes Mendelian Randomisation (discussed more fully in chapter 2) and randomised controlled trials. Providing randomised controlled trials have a sample of sufficient size, confounding factors are evenly distributed between the interventional and control arms of the trial by the process of randomisation. Associations between the intervention and the outcome, not seen in the control group, can more confidently be considered a result of the intervention rather than due to another factor. Randomised controlled trials do of course have their own limitations and appropriate critical appraisal methodology should be applied to any such investigations between coffee drinking and a health outcome. To date, there have only been a limited number of such trials that have been meta-analysed, each of short duration, and for easily measurable end points including blood pressure and lipid profiles. These were discussed in chapter 2.

Not all clinical outcomes would lend themselves to a randomised controlled trial. However, non-alcoholic fatty liver disease (NAFLD), in which liver fibrosis, cirrhosis, and hepatocellular carcinoma form a pathological pathway, lends itself to a randomised controlled trial where coffee could be given as a treatment. There are several suitable biomarkers[31,244,245] and imaging modalities[246,247] that could be used as surrogate markers for disease progression and the potential of coffee to beneficially change the natural history of disease progression could be tested.

A further issue in coffee research to date is bias. Bias can be broadly split into selection and information biases. Selection bias is concerned with systematic error in the selection of the study sample and will not be further considered at this point. Information bias results from some type of measurement error and can cause misclassification in which an individual participant's exposure, covariate or outcome variable may be incorrectly assigned[248]. This may happen for several reasons. In observational studies of coffee consumption, misclassification of coffee exposure is a possibility because of the challenges of ascertaining intake. This can be considered in two ways. Firstly,

misclassification caused by poor validity of instruments used to ascertain coffee intake such as food frequency questionnaires or food diaries. Secondly, the unit of measurement applied to exposure of coffee in the diet. In this context the cup has historically been used as the common unit of coffee intake. Not only is there no internationally recognised coffee cup size, the preparation method, including type of bean, roast, the strength of coffee and proportion of cup consumed, will all effect the true exposure of coffee for an individual.

To address these limitations of the cups/day measure, I created a coffee unit measure that catered for two of these variables, by taking into account different coffee preparation methods and cup sizes. I used this unit measure to evaluate the extent of misclassification in the cups/day measure when compared to a standardised cups/day measure using a representative sample of the UK population from the National Diet and Nutrition Survey (NDNS). The rationale for this work was to test whether a coffee unit measure could offer advantages in the classification of coffee consumption in a future randomised controlled trial in order to better ascertain baseline intake or guide the intervention assuming a pragmatic free-living design.

3.2 Methodology

3.2.1 Creation of a coffee unit measure

A standard coffee unit measure was created using published estimates of caffeine and chlorogenic acid concentrations (mg/mL) across different preparation methods from analyses of coffee shop or home prepared coffees. These are frequently found to have much lower caffeine concentrations compared with laboratory samples,[249] (Table 9).[22,250–257] Published laboratory estimates were used where these were not available. Chlorogenic acid concentrations were considered as a surrogate measure of all non-caffeine compounds within coffee. Specifically, diterpenes were not included in the coffee unit measure because they are in the order of 100 to 1000 times lower in concentration (depending on preparation method) compared with caffeine and chlorogenic acid. Equal weight was given to caffeine and chlorogenic acid and these were summed to produce a total concentration of active ingredients in mg/mL. One unit measure was defined as 227mL (8 UK fluid ounces) of instant coffee which is the most common type and size of coffee consumed within the UK – equivalent to a standard household mug. Other typical coffee drinks were derived as shown in Table 9 and these were calculated by dividing the

Table 9: Preparation type definitions, caffeine, chlorogenic acid and diterpene concentrations, one unit volumes and derived coffee unit examples

Coffee Preparation Type		CAFFEINE (CAF) mg/mL	Source	CHLOROGENIC ACIDS (CGA) mg/mL	Source	DITERPENES (Cafestol plus Kahweol) mg/L	Source	CAF + CGA mg/mL	Volume of coffee preparation type in 1 unit	Coffee unit of typical drink
Instant	(Concentrated brewed coffee granules or powder diluted with boiling water)	0.33 (0.10 to 0.56)[a]	21 home brewed[250]	0.51 (0.28 to 1.22)[a]	8 lab prepared[251]	3.8[bc]	3 lab prepared sampled in duplicate[252]	0.84	227 mL	1 unit in 227mL mug
Decaffeinated Instant*	(Instant with caffeine removed by processing)	0.01 (0.00 to 0.01)[a]	3 home brewed[250]	0.46	Assumed 10% less than caffeinated[253]	3.7[bc]	3 lab prepared sampled in duplicate[252]	0.47	406 mL	0.6 units in 227mL mug
Espresso	(Pressurised water passing through finely ground coffee)	3.11 (1.40 to 8.92)[a]	32 shop bought[251] (Scotland)	1.64 (0.22 to 10.54)[a]	32 shop bought[251] (Scotland)	4.6[bc]	5 lab prepared sampled in triplicate[254]	4.75	40 mL	0.7 units in 30mL espresso
Filter	(Coffee & water passing through a filter, commonly paper)	0.62 (0.22 to 0.75)[a]	14 home brewed[250]	0.81[bc]	1 lab prepared sampled in triplicate[255] (Arabica)	0.3[bc]	1 lab prepared sampled in triplicate [254]	1.43	133 mL	1.7 units in 227mL mug
French Press	(Also known as cafetière – coffee pot with plunger)	0.52[b] (Standard deviation of the mean 0.02)	3 lab prepared sampled in triplicate[22]	0.65[b] (Standard deviation 0.002)	3 lab prepared sampled in duplicate [256]	27.9[bc] (Based only on cafestol)	3 lab prepared sampled in duplicate[257]	1.17	163 mL	1.4 units in 227mL mug
Cappuccino	(Espresso & frothed milk)	0.72 (0.49 to 1.24)[a]	20 shop bought[251]	0.41[a] (0.06 to 0.99)	20 shop bought[251]	9.2	Extrapolated from espresso	1.13	169 mL	2 units in 354mL cup
Latte	(Espresso & steamed milk)	0.72	Extrapolated from cappuccino	0.41	Extrapolated from cappuccino	9.2	Extrapolated from espresso	1.13	169 mL	1.4 units in 240mL latte glass
Mocha	(Espresso & chocolate & steamed milk)	0.72	Extrapolated from cappuccino	0.41	Extrapolated from cappuccino	9.2	Extrapolated from espresso	1.13	169 mL	2 units in 354mL cup

*Other decaffeinated coffee types not included in table
[a] Median (Minimum to maximum)
[b] Mean
[c] Variability not available/calculable for combined measure

summed caffeine and chlorogenic acid of the preparation type and volume of interest by the caffeine and chlorogenic acid concentration of 227mL of instant coffee. For example, 30mL of espresso delivers 4.75mg/mL * 30mL = 142.5mg caffeine and chlorogenic acid which is equivalent to 142.5/(0.84*227) or 0.7 coffee units. Other examples include 1.7 units in a 227mL mug of filter coffee, 2.0 units in a 354mL cappuccino and 1.4 units in a 240mL latte.

3.2.2 Population sample

The UK National Diet and Nutrition Survey (NDNS)[258] data (years 5-8 (2012-16)) were used to quantify coffee intake in a representative sample of the UK population. The data is openly available via the UK Data Service (https://ukdataservice.ac.uk/). The NDNS includes the survey of approximately 1000 different UK adults and children per year on a rolling annual basis using a stratified random sampling strategy.[259] A four-day food diary is used to record all food and drink consumed and later coded and classified by researchers. Data was extracted from the NDNS for every adult participant (aged ≥18 years) who drank at least 1 cup of coffee during data capture. The number of cups and cup volume for each coffee type consumed was extracted.

Coffee preparation methods are broadly classified in the NDNS as instant, cappuccino, latte, strong infusion, weak infusion, and vending machine coffee. Espresso-based drinks such as cappuccino, latte and mocha are recorded in their own categories, but no separate category exists for espresso coffee. This was therefore categorised as strong infusion with volume <65mL, in keeping with typical volumes of single (30mL) or double (60mL) espressos. The remaining cups classified as strong infusions were combined with the cups classified as weak infusions and assumed to represent filtered (regular coffee). Vending machine coffee was assumed to be equivalent in composition to instant coffee. Cup volumes <15mL or >1000mL were excluded.

The complex sample function of SPSS (v24)[260] was used throughout the analysis to account for stratification, clustering, and weighting of the NDNS data to account for sampling and non-responder bias.

3.2.3 Ascertainment of misclassification

Misclassification was assessed by applying a) a standard cup volume and b) a standard cup volume and preparation type (coffee unit measure) to the intake of each participant to investigate the impact of using a cups a day measure when volume and preparation type have not been taken into account.

a) Standard cup volume

A 227mL volume-standardised equivalent number of cups a day was calculated for each participant and misclassification was calculated by subtracting the number of volume-standardised cups from the number of reported cups and rounding the result to the nearest cup. For example, if a participant reported 1 cup of coffee a day with a volume of 400mL, this would be equivalent to 400/227 or 1.8 volume-standardised cups a day. In this example the misclassification would be 1.0 minus 1.8 equals -0.8 cups a day (rounded to -1 cup). This is interpreted as reported cups underestimating actual intake by 1 cup.

b) Standard cup volume and preparation method (coffee unit measure)

A unit measure-standardised equivalent number of cups was calculated for each participant by summing total caffeine and chlorogenic acid (mg) for each coffee consumed and dividing by the single unit equivalent (i.e. instant coffee 0.84 mg/mL * 227mL).

For example, a participant reporting a 7-cup consumption comprising 4 cups of instant coffee at 250mL each, 2 cups of cappuccino at 350mL each, and 1 cup of espresso at 30mL, would have consumed:

4(0.84mg/mL * 250mL) + 2(1.13mg/mL * 350mL) + 1(4.75mg/mL * 30mL)

=840mg + 791mg + 142.5mg

=1773.5mg of total caffeine plus chlorogenic acid

To standardise to coffee units:

=1773.5mg/single coffee unit caffeine plus chlorogenic acid

=1773.5mg/(0.84mg/mL * 227mL)

=9.3 coffee units

In this example, reported intake underestimated actual intake by 2 cups, calculated by 7.0 minus 9.3 equals -2.3 cups and rounded to -2 cups.

The misclassification analysis was repeated separately for decaffeinated coffee using firstly 227mL caffeinated instant coffee, and secondly using 227mL decaffeinated instant coffee as the standard unit.

3.2.4 Subgroup Analysis

Misclassification was also calculated separately by gender, age group (18-34, 35-54, ≥55 years) and income tertile (≤£17,500, >£17,500 to ≤£32,383, >£32,383). Instant coffee as a proportion of all coffee consumed was also calculated for all caffeinated coffee drinkers and separately for each subgroup.

3.2.5 Sensitivity Analysis

Due to espresso being a small volume of highly concentrated coffee, the misclassification methodology was repeated separately by excluding espresso. Secondly, the analysis was repeated by substituting instant coffee of any volume with 30mL espresso coffee (volume-standardised to 30mL and a single coffee unit measure re-defined as 30mL espresso) to

model settings in which espresso is the most frequently consumed coffee type. Finally, to see how misclassification might change with changing composition assumptions of the unit measure, the analysis was repeated using ratios of caffeine to chlorogenic acid of 0:1, 1:0, 1:2, 1:3, 1:4, 1:5, 2:1, 3:1, 4:1, 5:1, 1:1:1 (diterpenes), and 1:1:1 (higher diterpenes: filter diterpenes replaced with French press diterpenes).

3.3 Results

There were 2832 adults in the 2012-2016 NDNS sample, and weighted, 62% of participants consumed any coffee over four days (comprising 54% caffeinated only, 4% decaffeinated only, and 4% mixed) whilst 38% consumed no coffee. The proportion of drinkers and non-coffee drinkers did not differ by gender. However, there were fewer coffee drinkers in the 18-34 age group and in the lowest income tertile (Table 10).

Table 10: Proportion of coffee and non-coffee drinkers by gender, age and income

Coffee drinking	All persons	Men	Women	Age 18-34	Age 35-54	Age ≥55	Income* ≤£17,500	Income* >£17,500 ≤£32,383	Income* >£32,383
Caffeinated	54.1	56.2	51.5	43.4	57.7	58.2	48.3	53.2	59.9
Decaffeinated	3.5	3.3	3.9	1.3	2.6	6.3	3.1	4.3	3.6
Mixed caffeinated	4.4	3.0	5.7	1.1	5.0	6.3	3.1	4.9	6.2
None	37.9	37.5	38.9	54.2	34.7	29.2	45.5	37.5	30.3
Total	100	100	100	100	100	100	100	100	100
Base (unweighted)	2832	1158	1674	744	1014	1074	698	647	773

* Data only available for 2118 participants; upper income tertile for years 7&8 of the survey was >£32,216

Cups/day and mean cup volume, by preparation type, are shown in Table 11. A total of 10,681 cups of caffeinated coffee were consumed during the diary period. Mean intake was 1.6 and 1.4 cups/day amongst caffeinated and decaffeinated coffee drinkers, respectively. Intake of coffee was marginally higher in men with a mean intake of 1.8 cups compared with 1.5 cups/day in women (data not shown). For those drinking coffee at least once daily the mean intake was 2.2 cups/day. The mean cup volume was 227mL and did not vary between daily and non-daily coffee drinkers. It also equated with the

mean volume of the most frequently consumed coffee type, instant coffee, which was consumed by 78% of caffeinated coffee drinkers and represented 75% of all coffee cups consumed. Filter coffee was the next most frequently consumed coffee type with 31% of caffeinated coffee drinkers consuming this at least once, with a mean volume of 224mL. Drinks such as latte, cappuccino, mocha, and espresso were consumed by fewer participants. Apart from espresso, these were typically consumed in larger volumes than instant coffee.

Table 11: Proportion of coffee drinkers, mean cups a day and mean cup volume by preparation type

Coffee drinking preparation types	% of caffeinated coffee drinkers by preparation type	% of daily caffeinated cups by preparation type	Mean caffeinated cups/day by preparation type (SD)	Mean caffeinated cup volume (mL) by preparation type (SD)	% of decaffeinated coffee drinkers by preparation type	% of daily decaffeinated cups by preparation type	Mean cups/day by decaffeinated preparation type (SD)	Mean decaffeinated cup volume (mL) by preparation type (SD)
Instant	77.9	75.1	1.6 (1.4)	227 (55)	84.8	86.5	1.4 (1.3)	217 (47)
Filter	30.7	17.2	0.9 (0.8)	224 (73)	18.9	10.9	0.8 (0.9)	230 (80)
Latte	12.3	3.3	0.4 (0.3)	269 (75)	4.6	1.1	0.3 (0.1)	270 (59)
Cappuccino	7.2	1.6	0.4 (0.2)	249 (67)	5.8	1.4	0.3 (0.1)	229 (31)
Espresso	4.9	1.8	0.6 (0.4)	40 (13)	0.6	0.1	0.3 (0.3)	40 (20)
Vending	2.3	0.1	0.5 (0.5)	197 (44)	-	-	-	-
Mocha	0.8	0.8	0.3 (0.2)	331 (115)	-	-	-	-
All types	100*	100	1.6 (1.4)	227 (64)	100*	100	1.4 (1.4)	219 (54)
Base (unweighted)	1623	10681	10681	10681	217	1198	1198	1198

*Sum of column exceeds 100% because many participants consumed more than one type of coffee

Most caffeinated coffee drinkers (69%) drank only one preparation type during the diary period. Two types were consumed by 27%, the majority of these drinking instant and one other type. Only 4% of coffee drinkers consumed three or more preparation types. For decaffeinated coffee drinkers, one and two preparation types were consumed by 85% and 14%, respectively.

3.3.1 Misclassification of coffee intake

When standardised by volume, 84% of participants had correctly classified reported intakes, 8% underestimated and 8% overestimated (Table 12) with most misclassification one cup in either direction. Two or more cups of misclassification accounted for only 2% of participants. The proportion of misclassification generally increased as reported cups a day increased. Unrounded, median volume misclassification was 0.00 cups (IQR -0.2 to 0.2). When standardised by the coffee unit measure, 73% of participant intakes were correctly classified, 22% underestimated and 5% overestimated (Table 13) and again most misclassification was for one cup in either direction. There was a marginal increase in the proportion of participants with two or more cups of misclassification accounting for 5% of participants. There was also an increase in the proportion of reported cups a day underestimating intake compared with misclassification of volume-standardised cups a day. Unrounded, median coffee unit misclassification was -0.1 cups (IQR -0.4 to 0.1). For decaffeinated coffee, 91% of participants had correctly classified volume-standardised intakes and 58% coffee unit measure-standardised intakes, with majority of misclassification overestimating intake by 1 cup, but increased to 90% when coffee unit measure was redefined as 227mL of decaffeinated coffee (data not shown).

Table 12: Proportion of participants misclassified across reported caffeinated cups compared with 227mL volume-standardised cups a day

Volume standardised cups a day	Reported cups a day											
	0	1	2	3	4	5	6	7	8	9	10	Total
0	13.80	0.98	0.06									14.83
1	0.07	38.96	2.24	0.16								41.44
2		1.41	19.64	1.93	0.17							23.14
3			2.36	6.76	0.47	0.21	0.03					9.83
4			0.30	1.27	2.91	0.63						5.11
5			0.01	0.43	0.86	1.32	0.19					2.81
6					0.23	0.66	0.55	0.21		0.03		1.68
7						0.09	0.19	0.14	0.11			0.54
8						0.05		0.01		0.14		0.21
9						0.07		0.02	0.02			0.11
10									0.21		0.02	0.24
≥11										0.09		0.09
≥2 cups over			0.06	0.16	0.17	0.21	0.03			0.03		0.66
1 cup over		0.98	2.24	1.93	0.47	0.63	0.19	0.21	0.11	0.14		6.89
No misclassification	13.80	38.96	19.64	6.76	2.91	1.32	0.55	0.14			0.02	84.10
1 cup under	0.07	1.41	2.36	1.27	0.86	0.66	0.19	0.01	0.02			6.84
≥2 cups under			0.31	0.43	0.23	0.22		0.02	0.21	0.09		1.51
Total	13.87	41.35	24.60	10.55	4.63	3.04	0.96	0.38	0.34	0.26	0.02	100.00
% Misclassification*	0.51	5.77	20.17	35.94	37.08	56.60	42.60	63.83	100	100	0.00	
Base (unweighted)	237	649	383	177	87	53	18	10	3	5	1	1623

*Within corresponding reported cups a day column

No misclassification 1 cup misclassification ≥2 cups misclassification

Table 13: Proportion of participants misclassified across reported caffeinated cups compared with coffee unit standardised cups a day (where 1 unit = 227mL instant coffee)

Volume and preparation type (coffee unit) standardised cups a day	Reported cups a day											
	0	1	2	3	4	5	6	7	8	9	10	Total
0	13.74	0.41										14.15
1	0.13	34.53	1.13									35.79
2		5.89	15.84	1.45	0.10							23.27
3		0.53	5.99	5.08	0.28	0.11						11.98
4			1.31	2.76	2.39	0.47	0.03					6.95
5			0.31	0.74	1.04	1.11	0.19					3.38
6			0.01	0.39	0.36	1.01	0.55	0.21	0.21	0.03		2.77
7				0.02	0.28	0.10	0.19	0.13	0.02			0.73
8			0.01		0.11	0.10		0.02		0.14		0.38
9				0.12	0.08	0.02		0.02	0.11			0.35
10						0.07					0.02	0.09
≥11						0.05				0.09		0.14
≥2 cups over					0.10	0.11	0.03		0.21	0.03		0.49
1 cup over		0.41	1.13	1.45	0.28	0.47	0.19	0.21	0.02	0.14		4.29
No misclassification	13.74	34.53	15.84	5.08	2.39	1.11	0.55	0.13	0.00		0.02	73.37
1 cup under	0.13	5.89	5.99	2.76	1.04	1.01	0.19	0.02	0.11			17.13
≥2 cups under		0.53	1.65	1.27	0.83	0.34		0.02		0.09		4.72
Total	13.87	41.35	24.60	10.55	4.63	3.04	0.96	0.38	0.34	0.26	0.02	100.00
% Misclassified*	0.94	16.5	35.6	51.8	48.44	63.55	42.60	65.75	100	100	0.00	
Base (unweighted)	237	649	383	177	87	53	18	10	3	5	1	1623

* Within corresponding reported cups a day column

No misclassification 1 cup misclassification ≥2 cups misclassification

3.3.2 Subgroup analysis

Table 14 shows the proportion of misclassification when using the coffee unit measure across different subgroups of caffeinated coffee drinkers. There were some notable differences with misclassification being greater in men compared with women, younger compared with older participants, and participants in the highest income tertile. Participants in the oldest age group and middle or lower tertile of income had the least misclassification. Caffeinated coffee drinkers in the lowest tertile of income drank 79% of all coffee cups as instant coffee compared with 56% in the upper tertile. Income rather than age appeared to drive most of the non-instant coffee consumption and by definition non-instant coffee consumption is likely to account for much of the misclassification.

Table 14: Misclassification of reported caffeinated cups a day compared with caffeinated coffee unit standardised cups a day across subgroups

Characteristic of participant	Base (unweighted)	Proportion (%) of misclassification of coffee consumption using coffee unit measure					Instant coffee as % of all coffee
		None	1 cup under	≥2 cups under	1 cup over	≥2 cups over	
Total	1623	73.4	17.1	4.7	4.3	0.5	72
Male	667	69.1	18.4	7.2	4.7	0.6	69
Female	956	77.6	15.9	2.2	3.9	0.4	67
Age 18-34	323	71.0	18.6	4.1	5.2	1.1	68
Age 35-54	613	68.5	19.6	6.5	5.1	0.3	64
Age ≥ 55	687	79.1	14.0	3.2	3.1	0.4	71
Income ≤£17,500* (T1)	405	78.5	12.2	3.5	5.5	0.2	79
Income >£17,500≤£32,383* (T2)	414	74.1	16.3	3.1	5.4	1.0	71
Income>£32,383* (T3)	598	68.1	22.9	6.1	2.9	0.0	56
Age 18-34 and income T1	88	71.0	14.7	2.7	11.3	0.4	77
Age 18-34 and income T2	92	68.6	16.2	5.7	6.1	3.4	77
Age 18-34 and income T3	119	73.2	23.3	3.2	0.3	0.0	57
Age 35-54 and income T1	119	69.7	14.7	9.2	6.5	0.0	75
Age 35-54 and income T2	167	73.5	17.1	1.9	7.1	0.3	70
Age 35-54 and income T3	267	62.9	25.7	7.8	3.5	0.0	57
Age ≥55 and income T1	198	85.8	10.1	1.4	2.7	0.2	81
Age ≥55 and income T2	155	79.4	15.3	2.6	2.7	0.0	70
Age ≥55 and income T3	212	72.0	18.6	5.7	3.7	0.0	56

* Income tertile data only available for 1335 of 1623 caffeinated coffee drinking participants; upper income tertile for years 7&8 of the survey was >£32,216

3.3.3 Sensitivity Analysis

When espresso coffee was removed from the analysis 85% and 74% of participants had no misclassification for volume-standardised and coffee unit-standardised cups a day respectively. This finding is similar to the main analysis. When instant coffee was substituted with espresso coffee, 40% of participants had no misclassification when volume-standardised, but 75% when using the coffee unit measure. When the ratio of caffeine to chlorogenic acid used to create the unit measure was varied, proportions of participants with no misclassification were relatively stable with 78% for 0:1, 71% for 1:0, 76% for 1:2, 77% for 1:3, 1:4 and 1:5, 70% for 2:1, 3:1, 4:1 and 5:1, 73% for 1:1:1 (both diterpenes and higher diterpenes).

3.4 Discussion

Published estimates of caffeine and chlorogenic acid across preparation methods were used to create a new coffee unit measure and this was applied to representative coffee consumption data from the UK population using the NDNS. Compared with volume standardised cups, 84% of caffeinated coffee drinkers had correct classification of reported cups a day measure, and 73% when using coffee-unit standardised cups a day that took preparation type into account. Most misclassification was under or over by only one cup. Misclassification by two or more cups was only present in 5% of participants. Most existing research between coffee and health has used cups/day as the measure of intake and it is therefore reassuring that there is a low level of misclassification. However, our analysis suggests classification of coffee consumption could be improved beyond the simple cups/day measure, since approximately 1 in 4 participants had misclassified intake when taking into account volume and preparation type.

Misclassification varied with gender, age, and income tertile. A greater proportion of misclassification was seen in men, younger participants, and participants in the highest income tertile. Misclassification is a measure of deviation in size or preparation type from the standard 227mL cup of instant coffee. Participants in the highest tertile of income had lowest instant coffee consumption as a proportion of total coffee consumption compared with lower incomes. Instant coffee represents a relatively inexpensive coffee preparation type. The price of one jar of instant coffee is similar to a single coffee shop bought espresso-based coffee. Other home prepared non-instant types using ground coffee or coffee pods/capsules, which would be classified as infusions in the NDNS data, whilst not as expensive as coffee shop cups represent a significant additional cost per cup compared with instant coffee. Younger participants in the lowest income tertile had a relatively high proportion of underestimated misclassification due to larger volumes of non-instant coffee compared with other subgroups (data not shown). Despite low income, younger people in the lower income tertile may be drinking more of their non-instant coffee outside the home environment where typically drinks are served in much larger volumes.

Actual coffee cup sizes consumed were distributed evenly around the 227mL standard volume suggested by the even proportion of participants with under or overestimation of coffee consumption when reported cups were compared with volume-standardised cups a day. This pattern was still present when espresso coffee was excluded from the analysis. This was because relatively few espresso coffees were consumed during the diary period. When instant coffee was switched to espresso and compared with a 30mL standard volume the proportion of volume misclassification increased substantially due to the non-espresso coffees of much larger size, whilst the misclassification using the coffee unit measure was relatively stable. Misclassification by volume is clearly affected by the choice of standard volume and this is especially important when intake includes espresso coffee, which is low volume but high concentration, compared with other preparation methods, and is the most commonly consumed coffee in some European countries.[261] The results highlight the superiority of the coffee unit measure over a volume only comparison across the range of preparation methods. The higher concentration of caffeine and chlorogenic acid present in the non-instant types of coffee preparation is captured by the use of the coffee unit measure as highlighted by a greater proportion of participants with underestimated compared with overestimated intakes.

When standardised to a unit measure of 227mL decaffeinated instant coffee, misclassification of intake among decaffeinated coffee drinkers was much less than caffeinated coffee drinkers, due to less deviation from size and type of decaffeinated

compared with caffeinated coffee. However, when standardised to a unit measure of caffeinated instant coffee the misclassification increased substantially, highlighting potential bias where studies have not differentiated between caffeinated and decaffeinated coffee when measuring coffee exposure.

There is uncertain impact of an approximate 25% misclassification of coffee consumption on the conclusions drawn by existing coffee research. Misclassification of exposure in this context is likely to be non-differential. This means that it will affect those with and without a health outcome equally and is generally understood to dilute the strength of effect estimates when the exposures are dichotomous, moving both beneficial and harmful estimates towards the null. However, it may be less predictable when there are more than two exposure groups.[262]

3.4.1 Strengths and limitations

The development of a coffee unit measure is a unique attempt to improve the classification of coffee consumption in participants of research studies and in the wider healthcare setting. However, the approach has several limitations. Firstly, published estimates of caffeine and chlorogenic acid concentrations used to create the calculate coffee unit measure equivalents for each coffee type are limited. In contrast to a unit of alcohol that is easy to define as 10mL (8g) of pure ethanol, the coffee unit measure was a composite measure of two compounds. Coffee is a complex mixture of hundreds of bioactive substances, with no scientific consensus that a single component is responsible for health effects. More likely there is a synergy between ingredients. Caffeine in isolation is likely to have different health effects compared with whole coffee. We used only two components of coffee to create a unit measure because these were available as a concentration (mg/mL) for a range of coffee preparation types. In the sensitivity analysis, varying the ratio of caffeine to chlorogenic acid, or adding in diterpenes, in the creation of the coffee unit measure made little difference to the proportion of misclassification.

There are many other factors in our analysis of the NDNS data that could not be accounted for, and we made assumptions regarding some of the preparation types. For example we assumed vending machine coffee was equivalent to instant coffee. Many

modern vending machines emulate the barista prepared espresso-based beverages such that vending machine coffee may have coffee unit concentrations more similar to non-instant coffee. The assumption that strong infusions under 65mL were espresso may have overestimated coffee unit intake if these were non-espresso coffees. However, vending machine and espresso coffee were a very small proportion of total coffee consumed and this is unlikely to have affected the results.

We assumed larger volumes of strong infusion, and all weak infusions, as filter coffee, but these may have been other types including French press (cafetière), Aeropress, or coffee pods. Such coffee types would have similar composition to filter coffee and our assumption is unlikely to have affected the misclassification identified substantially.

Incomplete consumption of coffee within each cup may have further affected misclassification although studies have suggested that these tiny amounts are unlikely to contribute significantly to this.[263] Furthermore, we cannot account for a number of other unmeasured factors including the strength of coffee due to variation in quantity of coffee grounds used, extraction by baristas, roast, or bean type (Arabica versus Robusta). Concentrations of caffeine and chlorogenic acids in the analysis of home and shop prepared coffee beverages varied widely. Even identical preparation methods using the same coffee in the same establishment on consecutive days have been found to produce coffee that varied in composition.[264]

The standardised coffee unit measure could be used in a randomised controlled trial to classify baseline coffee intake or quantify a target intake across preparation types. It could also be used in observational studies to improve the quantification of coffee intake. One potential drawback is the extra level of information required to generate the coffee unit measure, requiring estimation of volume and preparation method, and a suitable instrument to capture this information. A dose-response relationship has been identified between coffee and several health benefits, and future health advice may be based on reaching an intake threshold. A threshold based on coffee units rather than cups could reduce the issues associated with coffee cup heterogeneity.

In conclusion, a coffee unit measure is easy to construct and can be applied to a range of coffee preparation types. It could be used to improve the classification of coffee as an exposure and could be considered for use in studies that evaluate the relationship between coffee drinking and health outcomes, or in delivering future health advice.

Chapter 4: A mixed methods study - Exploring coffee consumption in people with non-alcoholic fatty liver disease and understanding barriers and enablers to increasing their intake (CUPLID)

4.1 Background

Before a randomised controlled trial can be conducted where coffee is evaluated as a treatment in people with NAFLD it is important to understand current patterns of coffee consumption that exist in this patient group, views about whether they think they would be able to drink more coffee, and perceptions on our proposed future interventional research. This can be achieved by a mixed methods approach - using qualitative thematic analysis of semi-structured interviews to inform final design of a survey questionnaire.

This research is important because firstly, there is no detailed knowledge about the pattern of coffee consumption in people with NAFLD. Whilst there is population level data on coffee drinking patterns from large nutritional surveys, such as the National Diet and Nutritional Survey in the UK, this has not been specifically ascertained in people with NAFLD. In existing observational studies, coffee intake data will have been collected at baseline in healthy participants of cohort studies before disease was clinically detected, or after diagnosis in case-control studies. However, ascertainment of coffee intake in such studies rarely extends beyond the number of cups consumed per day, and even this basic level of information has not been ascertained specifically in people with NAFLD living in the UK.

Secondly, as a bridge to a future randomised controlled trial, where we will ask participants to increase their coffee intake, it is important to know whether people with NAFLD would feel able to increase their coffee consumption beyond what they already consume, how this could best be achieved, and to understand some of the barriers and enablers that will influence this potential change in behaviour.

Based on the observational evidence to date, the intervention of a future randomised controlled trial may be aimed at optimising caffeinated coffee consumption at intakes of 4-5 cups per day for patients with NAFLD. Whilst it is possible that benefits in NAFLD may still occur at higher intakes, this level of consumption is associated with maximum relative risk reduction for a range of outcomes, and would also avoid potential physiological side effects of caffeine that may be experienced at higher doses. It is therefore envisaged that patients with NAFLD would fall into three groups. Firstly, there will be patients who do not currently consume any coffee (0 cups/day) who may benefit from the addition of coffee into their diet. Secondly, those drinking 1-3 cups/day who may benefit from the increase of coffee intake to 4-5 cups/day and thirdly, those who are already consuming ≥4 cups/day

of coffee, who would not need to change. However, we currently have no knowledge about the distribution of such patterns of drinking in patients with NAFLD. There is also considerable heterogeneity in the coffee cup measurement. Furthermore, as already discussed in earlier chapters, there is no universally recognised standard coffee cup size and the bioactive components of coffee in a single cup will vary depending on the type of bean (e.g. Arabica versus Robusta), degree of roasting and preparation method, including the quantity of bean, grind setting and brew type used. This implies that equivalent coffee cup consumption across individuals represents a range of intakes of bioactive compounds. Detailed consumption patterns in a population of patients with NAFLD could therefore allow some disentanglement of consumption by preparation type and cup size, in order to identify those patients who may benefit from increasing coffee intake, and therefore who would be eligible for inclusion in a future randomised controlled trial.

4.1.1 Theoretical framework

The theoretical approach for the present research protocol is based on the philosophical paradigm of pragmatism, that acknowledges the plurality of knowledge, and allows for non-relativist positive action[265]. Knowledge is viewed as being both constructed *and* based on the reality of the world we experience and live in[266]. In the context of the present research, this means the number of cups of coffee people drink, the preparation methods used and locations where they consume them, are data that can be counted and exist as a reality, and at the same time, the beliefs that lead them to choose this coffee drinking behaviour, attitudes they may have towards increasing their coffee consumption, and views about taking part in future research, are value-bound and based on the social and cultural context in which they live, and the experiences that they have had to date. Thus pragmatism is not committed to a single philosophical reality. Pragmatism as a philosophy has evolved in many different nuances but the work of classic pragmatists such as John Dewey is relevant to the current research proposal. Dewey philosophised that 'warranted assertions' (knowledge) resulted from taking action and experiencing the outcome[267]. Actions result from reflection on beliefs and beliefs result from reflection on actions. In the same way that this applies to everyday life it also applies for research in which our method of inquiry will result from reflections of prior actions that have stemmed from beliefs, and vice versa. In understanding the importance of knowledge interacting with action, pragmatism is orientated towards real-world practice and is therefore relevant to the present research inquiry in which the objective is ultimately to improve the health of

people with NAFLD. The approach emphasises a focus on the nature of the research problem and this informs the subsequent specific methodological, often pluralistic, approach[265]. Pragmatism as a paradigm assumes the freedom to choose the best methods and procedures that meet the objectives of the research in order to fully understand the research problem.

Following on from this, an effective method to best explore patterns of coffee drinking in people with NAFLD is to use a mixed-methods approach[265]. Mixed-methods combine elements of qualitative with quantitative research. Specifically, an exploratory sequential mixed-methods methodology will be used in which qualitative methodology will precede quantitative. This is because the qualitative component will allow data to be generated to help design and improve the instrument for data collection (survey) in the quantitative work (chapter 5). The qualitative research will provide a richer understanding of the pattern of coffee consumption in people with NAFLD and deeper exploration of perceptions of increasing coffee consumption, than would be possible with quantitative approaches alone, including, for example, the sole use of survey questionnaires. However, the quantitative component of the mixed-methods is also important to extend the investigation to a larger, representative, sample and gain a better understanding of the patterns of coffee drinking across a population of people with NAFLD. The theoretical framework and methodology is summarised in Figure 25.

Another dimension of theory relevant to the current enquiry is that of behaviour change. The overarching objectives of the research are bridging knowledge gaps towards a randomised controlled trial in which increasing coffee intake would be the likely intervention. Such behaviour change would also be encouraged in everyday life in the hypothetical situation in which coffee had proven benefit in NAFLD. One model of behaviour change is the COM-B behaviour change system[268], for which the central tenet is that behaviour (B) is influenced by the interaction of capability (C), Opportunity (O) and Motivation (M), and each factor is also influenced by the behaviour itself. Briefly, capability is the physical and psychological ability to change the behaviour, motivation encompasses all the brain processes that energise the change, both considered and automatic, and opportunity are all the factors external to the individual that make change a possibility. Understanding capability, opportunity and motivation in relation to people's current coffee drinking behaviour would arguably contribute towards developing the future intervention for effective behaviour change.

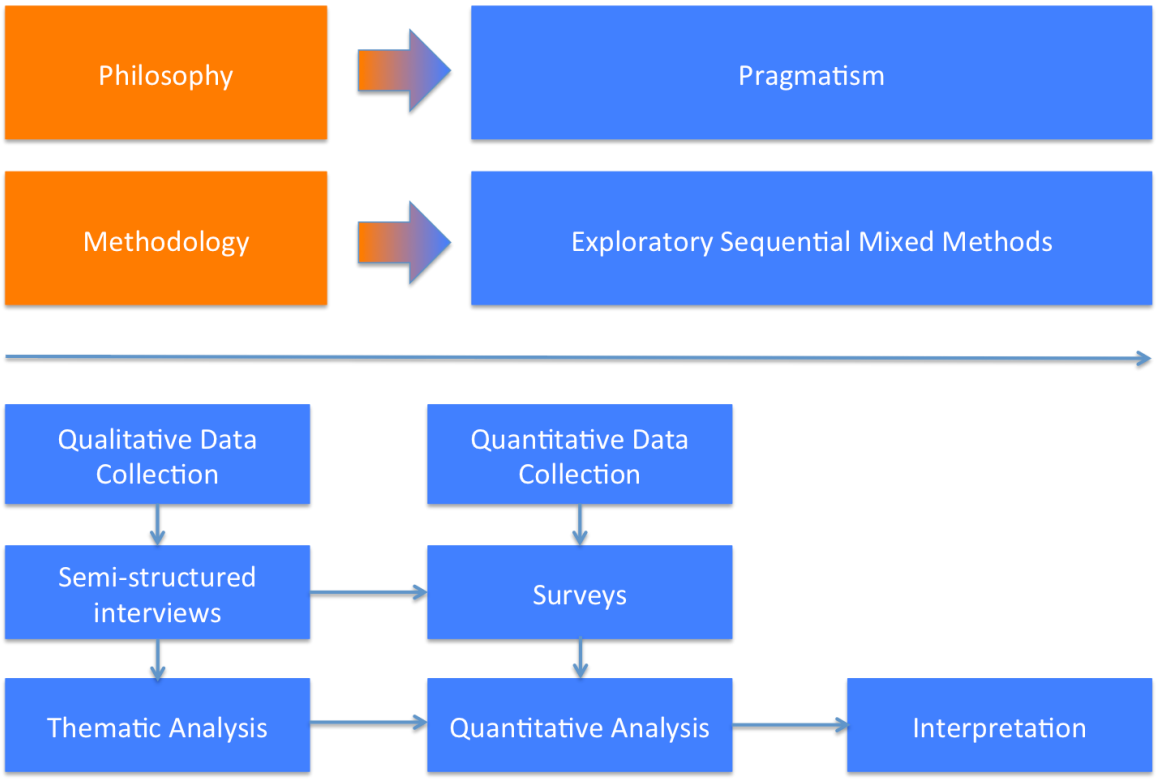


Figure 25: Theoretical framework and methodology of the CUPLID study

4.2 Research question

What are the patterns of coffee consumption in people with Non-Alcoholic Fatty Liver Disease (NAFLD) and what are the barriers and enablers to increasing their intake?

4.2.1 Objectives

In patients with Non-alcoholic Fatty Liver Disease (NAFLD), using mixed-methods research, including qualitative interviews and quantitative surveys:

- To investigate the pattern of coffee drinking (caffeinated and decaffeinated) including preparation type, frequency, volume, and location
- To investigate the pattern of non-coffee caffeine drinking including type of beverage, frequency, volume and location

- To investigate the pattern of additional ingredients consumed with coffee such as milk and sugar
- To explore whether coffee consumption has changed in people due to their liver condition
- To explore perceptions of barriers and enablers to increasing coffee consumption to inform intervention design
- To explore perceptions regarding the acceptability to patients of a randomised trial based intervention to drink more coffee

4.2.2 Qualitative phase

Outcomes

Key outcomes in the qualitative phase relevant to the research question:

- Patterns of coffee drinking (number of cups, size, strength, preparation method, location, additional ingredients)
- Perceptions of being able to increase coffee consumption in normal settings*
- Views on how increased coffee consumption would be achieved in normal settings
- Views on acceptability of being asked to increase coffee consumption as part of a research study*
- Views on acceptability of being randomised to drinking usual coffee or increased coffee consumption
- Perceptions of being able to increase coffee consumption in a research study
- Views on how increased coffee consumption would be achieved in research settings

* For the purposes of the present study, questions focused on increasing intakes from any baseline consumption, to an additional two cups/day

4.3 Methods

An overview of the qualitative methods is presented in Figure 26.

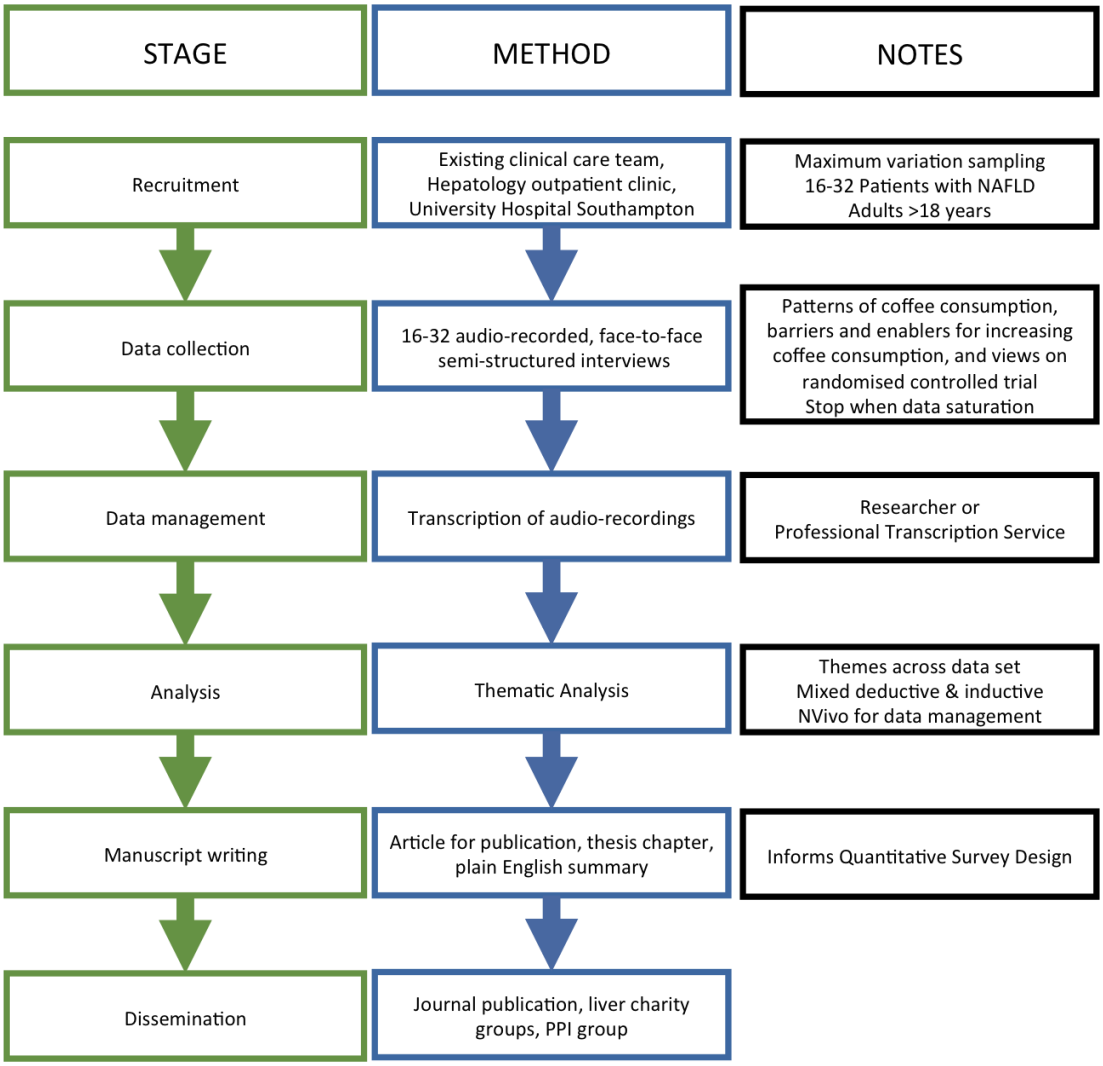


Figure 26: An overview of methodology in the qualitative phase of CUPLID

4.3.1 Qualitative data collection and setting

Semi-structured interviews were conducted to collect the data. Semi-structured interviews are an appropriate method to understand the experience of a phenomenon from the perspective of the participant and also address the research question. Participants were recruited via a single centre setting at hepatology outpatient clinics at University Hospital Southampton. Two regular clinics were accessed each week that were led by a consultant hepatologist with a particular interest in NAFLD. These clinics were chosen because they were run by the consultant hepatologist who was collaborating with the research project, and specifically should have a high caseload of patients with NAFLD. University Hospital Southampton was chosen because the Primary Care and Population Science Academic

Unit is embedded in the hospital as part of the University of Southampton. Prior to the start of each clinic, the researcher provided a recruitment pack for each clinician. Each pack contained a capture sheet for contact details of any potential participant and a participant information sheet. Only members of the existing clinical care team identified suitable patients. The researcher was either present in the clinic when there was spare room capacity, or contactable by telephone. Where possible, potential participants were seen immediately upon expression of interest and the protocol followed with regard to explaining the research in more detail and taking consent (for topic guide, consent form, and participant information sheet, see appendices C-E). Interviews were conducted in a clinic room in the outpatient area, a room in the MRC clinical research facility (also within University Hospital Southampton), or on the telephone depending on availability and participant preference.

Interviews lasted from 25-60 minutes and were all conducted by RP. Participants were also asked to complete an anonymised socio-demographic and behavioural characteristics questionnaire, either before or after the interview (appendix F). This included gender, age group, ethnicity, employment, house ownership, persons living in household, self-reported height and weight, self-reported diagnosis of heart disease, stroke or type II diabetes, self-reported cigarette usage, and self-reported alcohol consumption using an embedded Alcohol Use Disorders Identification Test for Consumption (AUDIT-C) questionnaire. This is a validated tool consisting of three questions to quickly identify harmful alcohol intake, where a score of <5 is considered low risk and ≥5 considered increased risk. AUDIT-C was included in the questionnaire to support understanding of alcohol intake across the group of NAFLD participants. As a token of appreciation, a £10 supermarket voucher, and a hospital car park exit ticket, were given to each participant at the end of each interview. Potential participants were made aware that these were included prior to their decision to take part.

4.3.1.1 Development of the interview topic guide

The semi-structured topic guide kept a focus on the research objectives but was flexible enough to allow exploration of unanticipated views from the participants, whilst also aligning to the exploration of behaviour change COM-B factors. The topic guide had been adapted following consultation with a Public and Patient Involvement (PPI) group of people who had experience of liver conditions or an interest in PPI. It was also revised

following appraisal by an experienced qualitative researcher. The topic guide was also re-ordered and redacted during the data collection period. Firstly, discussion about general and liver health were moved further back to allow rapport to be established before more sensitive subject matter, and to allow an immediate focus on coffee. Secondly topics of consumption of food containing coffee, or caffeine containing medication, were dropped as it soon transpired that most participants did not regularly consume enough coffee containing food, or caffeine-containing medications, to form a significant part of their regular coffee/caffeine intake. In its final form the topic guide was structured around patterns of coffee drinking, effects of liver disease/general health on coffee drinking, patterns of other caffeinated beverage consumption, perceptions of barriers and enablers to increasing consumption, and views about involvement in future research.

The interviews were audio-recorded using a digital voice recorder (Zoom H1), and transcribed verbatim by a professional transcription company Joe McGowan Transcriptions. However, the first two interviews were transcribed by RP to enhance familiarity with the data. The final interview, conducted on the telephone, could not be transcribed due to electronic interference creating a high-pitched buzz in the audio recording. However, the author listened to the recording and noted any novel ideas.

4.3.2 Eligibility criteria

Eligibility criteria are shown in Table 15.

Table 15: Eligibility criteria for participation in the qualitative phase of CUPLID

Inclusion criteria

• Males & Females
• Adults ≥ 18 years
• Any ethnicity
• Any socio-economic status
• Any coffee drinking status (coffee drinkers and non-drinkers)
• Diagnosis of Non-Alcoholic Fatty Liver Disease (NAFLD) by the existing clinic care team
  ○ Evidence of hepatic steatosis (imaging/histology)
  ○ No causes for secondary hepatic fat accumulation (medications, genetics)
  ○ Exclusion of significant alcohol consumption (<20g/day (2.5 units) women, <30 g/day (3.75 units) men)

Exclusion criteria

- Outside stated age range
- Not having a diagnosis of Non-Alcoholic Fatty Liver Disease (NAFLD)
- Unable to give consent

4.3.3 Sampling

A purposive, maximum variation sampling strategy was planned in order to maximise the variation of the sample for relevant participant characteristics. For the purposes of the present study, maximum variation in gender, age (dichotomised as 18-54 and >55 years) and coffee drinking status was planned. This would give a total of 8 variations and 2-4 participants per variation would result in 16-32 interviews. Data saturation was defined as the point when no additional information was being attained by further data collection, and when further coding was no longer feasible[269]. Analysis was conducted alongside data collection in order to identify data saturation. Data collection was stopped at a point of perceived data saturation although the sample only included three non-coffee drinkers and arguably data saturation may not have occurred in this subgroup. The maximum variation matrix is shown in Table 16.

Table 16: Maximum variation matrix

Age	**Gender**		**Coffee Drinking**	
18-54	Male	Female	Yes	No
≥55				

4.3.4 Qualitative data analysis

The qualitative data analysis was conducted using Braun and Clarke's[270] method of thematic analysis. This is a method for identifying, analysing and reporting patterns of meaning. Themes are essentially aggregations of key meanings present in the data which are relevant not by frequency of recurrence but by relevance to the research question. A mixed deductive and inductive approach was used where themes were drawn from those

that directly addressed the research question in addition to exploration of the raw data itself for emergent themes. The software package Nvivo[271] was used for data management. To arrive at themes, Braun and Clarke's six- step method was used. Familiarisation, the first stage, began during data collection because the author conducted all interviews. The author transcribed the first two interviews after they were conducted and all subsequent transcriptions were read and checked against audio recordings for inaccuracies. Coding, the second stage of analysis, was conducted along side the data collection for the first five interviews and a codebook was constructed which included definition of codes and examples. This was shared and revised with a second coder for the first five interviews agreeing a final version used to code the remaining dataset. Field notes were written by the author alongside interviews to capture additional research and reflexive insights.

Codes were used to create candidate themes and these were discussed with the second coder. The themes were then checked for consistency by reviewing against each code and against the entire dataset before themes were given final names and definitions. In addition to a reflexive practice, negative case analysis to avoid premature theme formation was used to safeguard rigor.

The findings from the qualitative study were used to inform the final design and content of the survey.

4.3.5 Ethical and regulatory considerations

The protocol for the mixed methods study and the related study documents, including the interview topic guide, consent form, and participant information sheet had been submitted and approved by the University of Southampton Research Ethics Committee, NHS Research Ethics Committee and the Health Research Authority. More details of these regulatory considerations are included in chapter 5.

4.4 Results

4.4.1 Patterns of coffee intake

There were 17 participants recruited in total. Fourteen were male and three were female. Additional characteristics of participants, including coffee drinking status, quantity, and main type of coffee consumed are shown in Table 17.

Table 17: Characteristics of participants in the qualitative phase of CUPLID

ID	Coffee drinker?	Gender	Age group	Ethnicity	Employment	BMI group	Diabetic?	Smoking	Audit-C Score	Coffee-type	Daily cups	Cup size	Milk	Sugar
G	N	F	55-64	White British	Employed	Obese	No	No	0	-		-	-	-
K	N	M	25-34	White British	Employed	Obese	No	No	0	-		-	-	-
P	N	M	35-44	White British	Employed	Obese	No	No	7	-		-	-	-
D	Y	F	35-44	White British	Employed	Overweight	No	Yes	6	Pod/capsule	4-5	Large household mug	None	1 tsp
M	Y	F	55-64	White British	Employed	Overweight	No	No	3	Instant/Filter	1-5	Standard household mug	None	None
B	Y	M	25-34	White British	Employed	Unknown	No	No	2	Americano	3-4	Standard household mug	Semi	None
Q	Y	M	35-44	Pakistani	Employed	Obese	No	No	0	Instant	1	Standard household mug	Semi	1 tsp honey
H	Y	M	35-44	White British	Employed	Obese	Yes	No	4	Instant	2	Large household mug	Semi	None
L	Y	M	35-44	Mixed	Employed	Obese	No	No	1	Pod/capsule	1	Espresso	Semi	1 tsp
E	Y	M	45-54	White British	Unable	Obese	No	No	5	Cappuccino	2-3	Large household mug	None	1 tsp
J	Y	M	45-54	White British	Employed	Obese	No	No	3	Pod/capsule	3-4	Standard household mug	Semi	1 tsp
I	Y	M	55-64	White British	Employed	Obese	Yes	No	7	Instant	3	Standard household mug	Semi	None
N	Y	M	55-64	White British	Employed	Overweight	Yes	No	4	Instant/Latte	2-4	Standard household mug	Semi	None
O	Y	M	55-64	White British	Employed	Overweight	No	No	2	Instant	4-8	Standard household mug	Skimmed	None
C	Y	M	65-74	White British	Retired	Obese	Yes	No	1	Instant	4	Standard household mug	Semi	1 tsp
F	Y	M	65-74	White British	Retired	Obese	Yes	No	1	Instant	3	Standard household mug	Semi	None
A	Y	M	65-74	White British	Retired	Obese	No	No	2	Instant	2	Standard household mug	Semi	None

Among the 17 participants, 14 were regular coffee drinkers and three consumed no coffee at all. Nine participants were aged between 18 and 54 years old and eight participants were 55 or over. There were fewer participants under 34. Most participants were overweight or obese and five had type II diabetes, known to be associated with NAFLD. One participant smoked cigarettes. Four of 17 participants had AUDIT-C scores consistent with higher risk of drinking, suggesting that both alcohol and fat may contribute towards their diagnosis, a group known as BAFLD (Both Alcohol and Fatty Liver Disease). Instant coffee was consumed by nine participants (64% of coffee drinkers) on a daily basis and ranged from 2 to 5 cups a day. One of these drank only decaffeinated instant coffee and the rest mainly consumed caffeinated varieties. Two participants had markedly different intakes depending on whether it was a working or non-working day. One would consume a single cup of instant coffee on working days, and up to five cups of filter coffee on non-working days. The other would consume four cups of instant coffee on working days, but on weekends would drink two espresso-based drinks such as Americanos and Lattes prepared at home. Three participants drank pod/capsule coffee on a daily basis, prepared with a machine in their homes, and a third participant drank mainly cappuccinos from a built in domestic coffee machine. A final participant drank mainly Americano style coffee made using a machine in their place of work.

4.4.2 Themes

Overarching themes and subthemes are shown in Figure 27 and Table 18, which also includes a definition of each theme.

Table 18: CUPLID themes, subthemes and definitions

OVERARCHING THEME		SUB THEME		
CAPACITY Ability to achieve an increase in coffee intake		Creating capacity		Suggestions for achieving increased coffee intake
		Substitution		Drinking coffee in place of other beverages
		Full to capacity		Perceived point past which no further coffee can be consumed
MOTIVATION The push and pull factors of coffee drinking		Coffee ritual		Routinised or habitual coffee drinking behaviour
		Preparation Type		Preference for different types of coffee preparation
		Taste		Enjoyment or aversion to the taste of coffee
		Brand		Preference for different brands of coffee
		Financial cost		Cost influencing choice of preparation, brand, or quantity
		Effort		Physical or psychological effort required to make coffee
		Reward		Coffee drinking as a reward, including social benefit
		Coffee and health		Views on coffee and general/liver health effects
		Health professional advice		Coffee drinking advice from a health professional
		Physical benefit		Perceived physical benefit from drinking coffee
		Physical disbenefit		Perceived physical disbenefit from drinking coffee
OPPORTUNITY Physical and situational circumstances which must exist in order for coffee drinking to be possible		Work		Opportunity for drinking coffee related to work
		Location		Opportunity for drinking coffee related to location
		Time		Opportunity for drinking coffee related to time
		Creating opportunity		Suggestions for creating opportunity to drink coffee
FLEXIBILITY Adaptability in coffee drinking behaviour		Demonstrates flexibility		Flexibility in coffee drinking expressed in the data
		Demonstrates inflexibility		Inflexibility in coffee drinking expressed in the data
FUTURE RESEARCH Acceptability and design of the proposed future research	**4.4.7**	Acceptability		Views on acceptability for intervention, randomisation and tests
		Design		Views on the nature of the intervention of increased coffee
		Assistance		Views on additional assistance needed to help drink more coffee

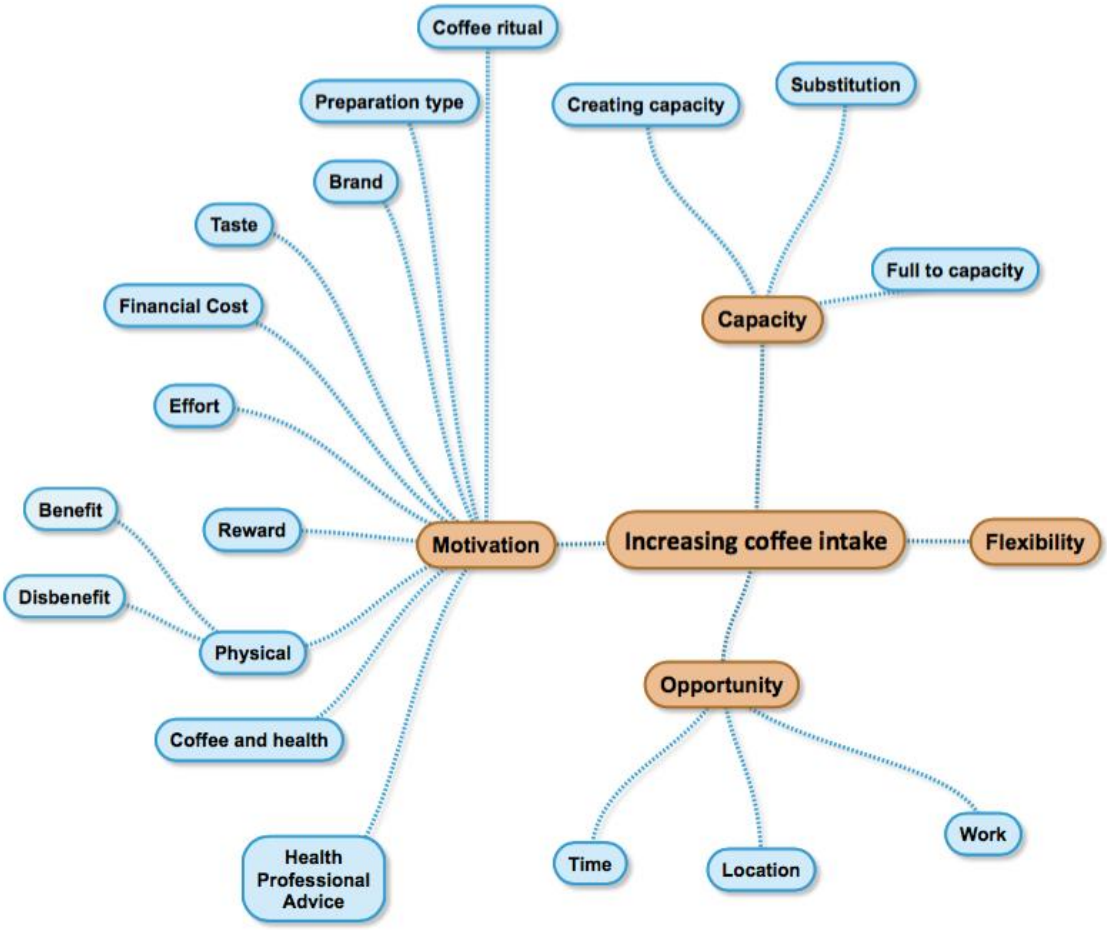


Figure 27: CUPLID Themes and subthemes in the qualitative analysis

4.4.2.1 Capacity – ability to achieve an increase in coffee intake

Capacity is an overarching theme referring to the ability to increase coffee intake. Certain factors will act to increase or decrease capacity for drinking more coffee. Coffee intake may reach a point of perceived saturation at which there is no capacity for any further consumption.

Capacity to increase coffee intake in a situation where the individual decided that they wanted to drink an extra two cups a day, and then if this was advised by a health professional, were questions specifically asked within the interview topic guide. The response to increasing coffee consumption by a suggested two cups a day was generally very positive, with most coffee drinkers in agreement that increasing coffee by two cups a day would be achievable.

> *'Oh, yes, if I wanted to, I could, definitely, yes. Yes, no problem at all.'[Participant I, Male, 55-64]*

4.4.2.1.1 Creating capacity

When invited to talk about the potential for increasing coffee consumption participants topicalised ways of creating capacity, and making changes in their lives that would allow them to achieve an increase in coffee consumption. There were a variety of responses with respect to how this would be practically achievable, many of which related to the theme of opportunity described later. Some participants described how they would elect to add extra cups of coffee into their daily routine earlier in the day in order to avoid caffeine related issues such as insomnia or increase in urine frequency during the night. However, some participants described delaying the coffee drinking until they had returned home after a day of work, not seemingly put off by the possibility of physiological disbenefit.

> *'Yes, no problem at all. I said to you, I don't drink it in the evenings. If I have a meal, I have a glass of water with my main meal. I can swap that for coffee, yes.' [Participant H, Male, 35-44]*

4.4.2.1.2 Substitution

Substitution was a commonly suggested method of creating capacity, where coffee could be substituted in place of other caffeinated or non-caffeinated beverages:

> *'Well, if that was the case I'd probably ditch the tea and just drink coffee all the time.' [Participant J, Male, 45-54]*

> *'Well I drink quite a lot of squash as well, so possibly rather than have a squash I will probably get on and have a cup of coffee.' [Participant M, Male, 55-64]*

It was also evident in some participants' usual total intake of caffeinated or non-caffeinated beverages, such that the increase in consumption of one led to the reduction of the other:

> *'It's a replacement. I wouldn't have my three cups of coffee if I've had several cups of tea.' [Participant B, Male, 25-34]*

However, the same participant suggested that in order to drink more cups of coffee they could reduce the size of the other coffee cups in compensation, perhaps defeating the object of increased coffee intake:

> *'Yeah, I'd just have a couple more normal size cups. If I was out and about and knew that I was going to have more I probably wouldn't have a large I'd probably get a regular sized one – I simply get a large one just because it lasts me longer - so If I thought I was going to get another coffee at the end of the shopping trip, I think I'd just get a medium sized one.' [Participant B, Male, 25-34]*

4.4.2.1.3 Full to capacity

Full to capacity refers to a participant expressing a point at which they could not drink any more coffee on a particular day. For one participant this was not a physical sense of fullness as in having a full stomach, nor directly related to physiological effects attributable to caffeine, but to more of a taste experience that had been interpreted as having reached a point of coffee saturation:

> *'Yes, I get to the point and it can be three cups some days, it can be five cups other days, where I've had my coffee fix, I'm done for coffee. I go around my partners and he'll say coffee, and I'm like, 'No, I'm coffeed-out, done'' [Participant D, Female, 35-44]*

Following on from this, the same participant felt that they would not be able to increase their coffee consumption:

> *'I don't think I could…I can't always physically stomach too much coffee. Just like anything, if you were told that you had to drink ten pints of fresh orange juice, even if you liked fresh orange juice, you couldn't physically force the last one or two down, even if it was your favourite drink. If you have something too extreme you can't enjoy it then, and I wouldn't enjoy another pushed one or two cups of coffee.' [Participant D, Female, 35-44]*

4.4.2.2 Motivation: the 'push' and 'pull' factors of coffee drinking

Interviews invited participants to discuss their motivation for drinking coffee, or not, and this framed the major push and pull factors for coffee drinking. Subthemes within motivation include coffee ritual, preparation type, taste, brand, financial cost, effort, and physical benefit and disbenefit.

4.4.2.2.1 Coffee ritual

When discussing their coffee drinking participant narratives oriented towards individual coffee rituals as they described the degree of routine or habitual intake of coffee. These habits tended to include the number of cups consumed on a daily basis, the preparation type, brand, and the location of consumption, and together created a *baseline regular intake*.

> *'Yes, well, I have one with my breakfast in the morning, one about half-past-12, and I have one about mid-afternoon, one after dinner, about 7 o'clock, and then I have an orange juice to take some medication with in the evening.' [Participant C, Male, 65-74]*

> *'I suppose you get used to it. It's part of the routine. Working in an office, I think you get used to drinking coffee...' [Participant N, Male, 55-64]*

Participants who described consumption that appeared to be ritualised also appeared to have quite stable intake over time and well established *baseline regular intake* would by definition be a motivating factor for consumption, but could also affect how flexible a participant might be in increasing coffee intake. This *baseline regular intake* was layered upon by an *opportunistic variable intake*, the degree of which varied across participants, and was influenced by many of the additional factors described under motivation and opportunity. The degree to which *opportunistic variable intake* replaced or added to *baseline regular intake* also varied across the dataset. For example for some participants, coffee consumed as *opportunistic variable intake* could replace coffee in the *baseline regular intake*:

> *'Yes, we would probably have a [branded coffee], in lieu of the one at home.' [Participant N, Male, 55-64]*

Opportunistic variable intake was also less frequent than the habitual intake and would likely to have a greater influence on average weekly or monthly, rather than daily, quantification of coffee intake.

For those employed, there was evidence that *baseline regular intake* varied depending on whether it was a working day or not. For some, non-working days created opportunity to drink more coffee, and/or coffee of a different preparation type, and for others, being away from the workplace meant drinking less coffee.

4.4.2.2.2 Preparation type

Different coffee preparation types have been previously described in chapter three. Participants varied in their preference towards, and therefore their exposure to, different coffee preparation types. Preparation type in of itself could be a motivating factor towards or away from drinking coffee. This could be driven by a number of factors including habits embedded within a *baseline regular intake*, or driven by taste and financial considerations.

Participants drinking only instant coffee as their *baseline regular intake* appeared to have less exposure to non-instant coffee types:

> *'Very infrequently do I use a coffee shop. The only time I tend to drink coffee out is when we might be travelling down to France. Then I'll have a coffee then, which is the favourite one there, the one without the milk, it's…' [Participant O, Male, 55-64]*
> *'Espresso-type?' [Interviewer]*
> *'Expresso [sic] yes.'*

Or non-instant coffee was something that other people drink:

> *'The espresso machines yeah – they don't do it like we do it do they' [Participant A, Male, 65-74]*

Most participants consumed a limited variety of different preparation types on a regular basis. Those who had some form of coffee machine in their home were more familiar with

the range of possible coffee preparation types and were less likely to drink instant coffee out of choice.

> *'Only ground beans. You know, in a machine and ground. Not out of a jar. Very rarely [instant], because we've got a proper coffee machine at home, and it tastes so much better than out of a jar.' [Participant E, Male, 45-54]*

The same participant also had concern about how processed instant coffee was:

> *'But is it better for me to drink organic coffee beans, ground, than it is to have a factory-made coffee which has been brewed by - I don't know what they do, freeze it and grind it, or - and what they put in it to keep it like that. To me, that's going to have more other things in it which is more detrimental to my health than just a natural coffee bean ground.' [Participant E, Male, 45-54]*

Participants also varied in how much detailed knowledge they had on how their coffee was made, but all had an appreciation that caffeinated and decaffeinated coffee were different. Decaffeinated coffee was a positive option for some participants, motivated by the belief that it was a healthier choice, especially when a participant described an additional health condition:

> '*The doctors told me that if you go down to decaf it's a lot better for you than ordinary coffee. Its not so strong.' [Participant A, Male, 65-74]*

For others decaffeinated coffee was perceived as a negative choice and avoided completely, either with the impression that it was more processed and therefore much less healthy, or had a distinctly unpleasant taste.

'Oh God no. No, no. no. If you're going to have a cup of coffee you might as well have a cup of coffee.' [Participant B, Male, 25-34]

'Decaffeinated, however, has had something taken out of it so it's not natural and I think it's wrong. There's no point in having coffee if it's decaf. Anything natural, I think's fine. If it's grown, it's not cultured, and it's not changed or had chemicals added then how can it be bad for you?' [Participant D, Female, 35-44]

4.4.2.2.3 Taste

Most coffee-drinking participants described an enjoyment of the taste of coffee as a key driver of consumption:

'I like the taste of coffee, obviously, or I wouldn't drink it. A lot of people don't like it because they think it's bitter. I don't have a lot of sugar in it either, so it is purely the coffee I like' [Participant D, Female, 35-44]

An aversion to the taste or the smell of coffee was also the key reason for those not drinking coffee to avoid it.

'*Just don't like the taste' [Participant P, Male, 35-44]*

'No, I really don't like the smell of it. I'll go past a coffee shop, [branded coffee shop] or something like that, and I'll normally go across the road because I don't like the smell.' [Participant G, Female, 55-64]

Even among established coffee drinkers, some types of coffee, such as decaffeinated also provided an unpleasant taste experience:

'I've got a jar of decaffeinated coffee at home which I've had for a while. I bought it because it was reduced. It was [supermarket] own brand, but as soon as I tried it I could taste the difference straight away. I could definitely taste the difference between my standard coffee, and I tried the decaf one in the morning one time, tried it once, and I put it away.' [Participant H, Male, 35-44]

Many participants described acquiring a preference in taste for non-instant coffees, often a result of having introduced a coffee machine into their home. This resulted in complete avoidance of instant coffee for some, whilst others quite happily would drink instant and non-instant coffee types where choice was influenced less by taste but by opportunity or effort.

Many participants had a preference for freshly ground coffee rather than instant coffee, although would still drink it on occasion:

'I enjoy coffee, preferably filtered coffee and I generally drink it black; however I enjoy a cappuccino or a latte. I enjoy a cold latte as well. I drink instant coffee. I don't enjoy that taste as much as I do a filtered one, but coffee, I do enjoy drinking coffee.' [Participant M, Female, 55-64]

Even within the preferred preparation type, coffee could be made poorly, and this could affect the taste. Coffee needed to be strong enough but not bitter.

'Americano again which was awful. It was just dreadful. It was watery.' [Participant J, Male, 45-54]

'Well, these are all manufactured by [coffee brand], but ask me the question of which coffee shop would I choose to go in to. I'd rather go into a [branded coffee shop 'A'] than a [branded coffee shop 'B'] because I find [branded coffee shop ,B,] coffee very bitter. I don't like bitter coffee and I never have those very powerful shots.' [Participant J, Male, 45-54]

The taste of coffee could also affect the motivation to drink additional coffee:

> *'It's just the type of coffee, again, it's got to be a nice coffee to sort of get on and make another cup.' [Participant M, Female, 55-64]*

Coffee had to also be served at the correct temperature for maximum taste enjoyment. Some would discard the contents of a partially consumed cup if it got cold:

> *'[Did not finish the whole cup] Cause it got cold. Problem is, at work, somebody would make me a cup of coffee, and obviously then I get busy and I focus on what I'm doing and I don't focus on anything else and my tea or coffee goes cold, I won't reheat it because I think that's absolutely vile' [Participant B, Male, 25-34]*

Another participant did not enjoy hot coffee and would reduce the temperature by adding lots of cold milk and reducing the volume of boiled water used to make their instant coffee:

> *'I don't like hot coffee… I'll boil the kettle, pour the water in, pour it halfway up to the halfway of the cup, and put the rest in of [cold] milk.' [Participant H, Male, 35-44]*

4.4.2.2.4 Brand

Brand is another subtheme of motivation and closely linked to taste, and financial cost, with preference for some brands, and avoidance of others. This included brand of preparation for use at home:

'I tend to buy the [coffee brand A]. Sometimes, the [coffee brand B], with the big pushed out lid. I do like that, and I do tend to, when I buy that one, you've got the [brand], but I tend to go for the stronger roast of coffee, because you've got different strengths. I did tend to like that, but it depends what's on offer. I'm not a [coffee brand] lover, not at all...I just don't think it represents coffee in a good way. It's okay, but there are better coffees out there at about the same price.' [Participant H, Male, 35-44]

Brand could also influence coffee experiences away from home:

'In terms of what coffee I get it does, yes, because if I'm working then I have my instant, but I can only have good instant. If I'm at home then, yes, I'll [pod machine]. If I'm out then it would be [branded coffee shop], or any of them, [branded coffee shop], [branded coffee shop] is my favourite, so anywhere that sells coffee, proper coffee, black.' [Participant D, Female, 35-44]

The same participant had a favourite coffee shop in different shopping locations:

'So, it would probably be, if I couldn't go to [branded coffee shop], then it would be where I know makes a good coffee. If I was in Eastleigh, there's a coffee shop [branded coffee shop] I'd go in there. If I was in town it would be [branded coffee shop], but only the one in West Quay. I'm a real coffee snob. So, it would be [branded coffee shop], I won't go to [branded coffee shop] because they're rubbish. Yes, [branded coffee shop] really, unless it's a café that I know makes good filter coffee. There is a couple about, there's a good one in Eastleigh*, there's a good one in Portswood*. There's a good one in Gunwharf* Quay!'*

It was not possible to differentiate whether preference for brand was purely based on taste, financial cost, or brand loyalty, in itself driven by many reflective and automatic processes, and it is more likely that all these factors interact to motivate participants towards specific brands and away from others.

4.4.2.2.5 Financial Costs

Coffee was often considered expensive, especially coffee consumed away from home in branded coffee shops. For some, this perceived excessive retail price meant avoidance of any coffee shop purchases at all, or limited to an occasional treat, and away from home coffee purchases tended to feature as *opportunistic variable intake* rather than daily *baseline regular intake*.

> *'Then, because I always liked a coffee when we went out, like to a [branded coffee shop], and you'd think, oh, that's really nice coffee. When you're out you have one. But now we've got the machine, or we've had the machines at home, it's sort of when you go out you think, God, £3.80 for that! I can go home and have one.' [Participant E, Male, 45-54]*

> *'The only thing I would say, I wouldn't drink coffee out and about, when I'm in town, but I'm partly… I'm not tight, but I won't pay the prices at [branded coffee shop]! If I'm going to have coffee, I'll have it when I get home.' [Participant H, Male, 35-44]*

Cost could also influence choice of brand of coffee purchased for home consumption:

> *'Yes, I mean, obviously, if I go shopping and there's a special on with one of the other ones, I think one's called [coffee brand], we get that as well. Yes, we just pick up whatever's there, but I never go for any other expensive ones, the [coffee brand], or anything like that. I don't do that.*' [Participant I, Male, 55-64]

The financial cost of coffee could also influence the preparation type offered to others, such as when entertaining at home:

> *'Yes, a big [filter machine] one. If I'm making coffee for a lot of people then [coffee pod brand] gets expensive, so the coffee filter machine comes out and then*

ground coffee.' [Participant D, Female, 35-44]

4.4.2.2.6 Effort

Effort was a motivating factor towards or away from coffee drinking, either affecting choice of coffee as a beverage in itself, or of the preparation method. There was a view from some that the act of making a cup of coffee was an effort, sometimes avoided, especially when there were other people to make coffee for at the same time:

'Um, normally, I'm going to sound like a right stingy git now, um, if I've got other members of the team with me who I know will drink coffee in the kitchen, I'll deliberately make tea so I don't have to stand there grinding all the stuff up for ages, because I can't be bothered because I'm lazy. No, its cause I just want to get back and do my job, no, If I'm rushed for time I'll have a cup of tea as opposed to a cup of coffee.' [Participant B, Male, 25-34]

4.4.2.2.7 Reward

Coffee drinking was associated with taking a break from work and some participants envisaged additional advantages of drinking more coffee because of the additional breaks. Shared experiences, such as going out for a coffee with work colleagues at lunchtime, or a break from a shopping expedition, were described, suggesting some social benefits of consumption.

'If my other half if she decides she needs to do some shopping in town, normally the bargaining point is that I get a cup of coffee out of it [laughter] otherwise it ain't happening' [Participant B, Male 25-34]

For one participant shopping trips were even planned around locations of coffee shops:

> *'No, we still have a coffee when I'm out sometimes, if we're out shopping or something, and I judge the routes by the coffee shops normally!' [Participant E, Male, 45-54]*

Coffee could even act as a reward for working:

> '*That's a treat for me on a Friday when I do a late shift is a Mocha' [Participant D, Female, 35-44]*

4.4.2.2.8 Coffee and health

The effect coffee might have on general, or liver health, was an area in which most participants expressed uncertainty. Some had never considered the effect it may have on their health and had no knowledge regarding the possible health effects:

> *'To be truthful, I've never really thought about it. There's so many things that are good and bad for us nowadays that we never knew when we were children and youngsters, so, I'm not one of these people that I'm over health conscious, that as soon as someone says something, I run to the nearest shop. I'm not one of them, so, no, I think it's pretty much always been the same.' [Participant I, Male, 55-64]*

None expressed any prior knowledge that coffee may be beneficial to liver health. When participants had some prior belief about coffee and health it tended to follow the traditional view that coffee was an unhealthy component of the diet:

'No, I've never heard that coffee… I know you shouldn't have too many cups of coffee, and the caffeine and all the rest of it, but I've never heard anyone ever say coffee could be beneficial. It's quite a new idea!' [Participant G, Female, 55-64]

However, some participants acknowledged the more recent shift in scientific opinion, promoted by the media, that coffee could be part of a healthy diet:

'Now you say that, I've read articles in the past, one the internet, and magazines, I've heard it on BBC News Breakfast, that coffee is a good thing, and I believe it is a good thing. [Participant H, Male, 35-44]

Another found the media coverage to suggest detrimental health effects:

'Well, personal feelings, I'm fairly agnostic about it. You obviously hear a lot of noise, like in the BBC and stuff like that, where every so often they get a report which then it's misinterpreted and you get big headlines. You have the general impression from the media that coffee is bad for you, but personally I'm fairly agnostic.' [Participant O, Male, 55-64]

There was also a feeling that media opinion changed regularly:

'There seems to be conflicting evidence from what I hear. It almost seems to depend which newspaper you read - do you know what I mean? I get the sense it seems to change. So no, overall, I'm not quite sure, if I'm honest; because, like I say, it does seem to vary.' [Participant P, Male, 35-44]

A few participants had health beliefs about coffee and specific health outcomes:

'If I'm completely honest with you I don't know. Um, I've heard things that it can give you kidney stones or something. That's why subconsciously I've always said I'll only have a couple of coffees a day because we've got a lot of stones in the family.' [Participant B, Male, 25-34]

'The reason why - I would most probably drink more, and sometimes I do drink more; it depends if people are round or whatever, but it's because I was told that it interfered with my - because I've got blood pressure tablets, so I wasn't too sure if it's good for me to do it or not, or too much caffeine; I don't know, so I sort of limit it.' [Participant E, Male, 45-54]

Many participants expressed awareness that certain additional ingredients, especially sugar, created a much less healthy type of coffee.

'All right, adding loads of sugar to it in a cup, then it's not a good thing….but a coffee by itself, as its supposed to be, coffee and milk, yes, I think it's good for you.' [Participant H, Male, 35-44]

'If someone's having eight cups of coffee a day I don't think that's healthy, if I'm honest, because a lot of people like milk in their coffee as well so then you've got the added extras.' [Participant K, Male, 35-44]

This extended to some participants who were more mindful of the potential detrimental effect of additional ingredients on their liver health:

'Its made me think twice about having lattes or mochas because obviously they're full of milk which is quite crap for you if you've got a fatty liver isn't it. So in that respect it's the only thing that's made me question it, or question how I have my coffee, not necessarily how much I have, just how I have it, I guess.' [Participant B, Male, 25-34]

The hypothetical scenario that drinking more coffee would benefit liver health appeared to be a motivating factor in perceptions of being able to increase coffee intake by two cups a day:

> *'I think probably consciously a yes if I thought it was going to sort of get rid of any problems I had with it, then yes, I probably would.' [Participant M, Female, 55-64]*

> *'I'd find a way of drinking them. I know my coffee max at the moment but if someone said, 'Oh, if you drink two more a day, then you won't have fatty liver disease now,' or I won't have any more pain, or this isn't connected to something else, then obviously I'd find a way of drinking the two extra cups of coffee, wouldn't I?' [Participant D, Female, 35-44]*

The additional motivation from a health benefit could overcome avoidance due to the effort required to prepare coffee:

> *'If I was advised to have more coffee then the chances are I'd probably drink coffee at home as well. I simply don't make it at home because I can't be bothered. [laughter] I'm quite happy to sit and have a pint of squash.' [Participant B, Male, 25-34]*

Motivation from apparent benefit to the liver extended even to those drinking no coffee at all. All three participants in this situation expressed a desire to overcome the dislike for the taste of coffee, treating it more like a medicine, or hiding the taste by using coffee as an ingredient during cooking:

> *'I could give it a go. I don't like the taste, if I'm honest, but I'd suck it up if it was a case of being healthy so absolutely, yes, I'd do that; two cups of coffee.' [Participant K, Male, 25-34]*

> *'I don't know if I'd drink it because I really don't like the flavour, but I would put it in something that was strong in flavour. I've heard of this kind of thing being done*

before. When I'm having chilli, I can put some coffee in my chilli mix, or my curry mix, because I wouldn't taste it, because that would overpower it, but it would mean I would consume some.' [Participant G, Female, 55-64]

The same participant suggested it could be treated like a medicine:

'If it was going to do some good, yes. It's a bit like taking medicine, isn't it? You take Night Nurse, it tastes disgusting, but if it's going to help you, you take it. I'd treat it in that way, almost like a medicine.'

One of the participants imagined that gaining a like for the unpleasant taste of coffee would be similar to that of alcoholic beverages, an acquired taste which may even be enjoyed after repeated consumption:

'It's a bit like when you're a kid and you have medicine and it tastes horrible; you've just got to gulp it down and then you have a sweet afterwards. I'll be honest, it may be that when you're a kid and you taste alcohol you go, 'Urgh!' Maybe if I start drinking it now I'd like it' [Participant P, Male, 35-44]
'So you think you would be able to break through that taste barrier?' [Interviewer]
'Oh yes. I'm sure if it was proven that it had a beneficial effect - yes, certainly.'

4.4.2.2.9 Health professional advice

Participants spoke of the importance of a health professional's endorsement of coffee drinking for health as a motivating factor for consuming it:

'If someone was to say, a healthcare professional said, 'We think coffee is beneficial to your liver condition, the fatty liver, and we'd like you to drink two extra cups per day' do you think that would change whether you would be able to or not?' [Interviewer]
'I'd almost certainly change. I would probably buy shares in one of the coffee companies as well!' [Participant F, Male, 65-74]

The question of whether they had received such advice, or advice to the contrary, was specifically within the interview topic guide. None of interviewees had received direct advice from health professionals with regard to changing their coffee consumption, other than given advice that decaffeinated coffee might be healthier for them, but this was not common. One participant had made changes specific to their own coffee drinking after a diagnosis of high blood pressure but said they had proactively changed their consumption and had not received such a recommendation from a health professional.

> *'Yes, I like it enough that I'll drink it a lot more if I didn't think it would affect my blood pressure. I'm medicated for my blood pressure. The idea of negating what the medication's doing by pumping in loads of - I don't think that the medication's going to necessarily negate too much caffeine intake, so I try to control myself.' [Participant L, Male, 35-44]*
> *'Have you been given that advice by a health care professional?' [Interviewer]*
> *'No, it just makes sense, I think that's why - I just don't want to negate'*

4.4.2.2.10 Physical benefit

Physical benefit captures participant accounts about the desirable physical side effects of drinking coffee, factors that moved people towards drinking it, or affected quantity or timing of intake. Some participants described additional energy or alertness as a useful effect of drinking coffee:

> *'Sometimes, I feel that um with a cup of coffee I get a little bit of, I wouldn't say a buzz out of it, I get a bit more energy – the energy comes back into me a bit.' [Participant A, Male, 65-74]*

'I started drinking coffee because I thought it would give me that little boost to start with, and then I discovered I actually quite, I quite like the flavour of it, so it is simply, unless I am shattered and I have an espresso, it is generally just because I enjoy drinking it, not for any other reason than that, unless I am tired, and then I'll have one to try and wake myself up.' [Participant B, Male, 25-34]

4.4.2.2.11 Physical disbenefit

Physical disbenefit captures participant accounts about the undesirable physical side effects of drinking coffee, factors that moved people away from drinking it, or affected quantity or timing of intake. Commonly insomnia, or an anticipation of insomnia, were key drivers away from consuming excess coffee. Such concerns also influenced the timing of coffee intake with avoidance after a certain time during the day.

'*Um. I drink it mainly at work, um, and during the day. I don't drink coffee in the evening just in case the caffeine makes me stay awake. Um. I try and limit myself to no more than three or four cups a day because again I don't want to stay up all night.' [Participant B, Male, 25-34]*

'Yes, so coffee will always tend to be around, between ten and midday. Never earlier and seldom later, because I don't sleep well either. Like I said, the last few years I've had a bunch of just health kind of issues. If I have a coffee, anything past seven pm, I survive on four hours sleep a night anyway, if I have a coffee in that, I can forget that.' [Participant L, Male, 35-44]

Insomnia could affect wellbeing and this was an important consideration when thinking about drinking more coffee:

'I don't think I could [drink more coffee than I currently do]. It would affect the other psychological sides of things. I need to sleep. I don't sleep anyway.' [Participant D, Female, 35-44]

The concern that coffee could cause insomnia was not a universal issue:

'[Coffee would not keep me awake] I could have one at midnight and I'd still go zonked out' [Participant E, Male, 45-54]

Additional trips to the toilet to pass urine were another physical disbenefit described by some participants:

'I would probably choose not to drink anything, whether it's coffee, tea, water, beer after 9 o'clock at night because I don't want to get up in the middle of the night, spend a penny! I've reached that age.' [Participant J, Male, 45-54]

'Yeah. There's certain times - I don't drink tea or coffee in the evenings. Purely because I would be up and down to the toilet all the time. So I don't do that. I do go to the loo a little too often. As you get older that does happen. Um. That's why I don't consume a lot of tea or coffee.' [Participant A, Male, 65-74]

For some, coffee consumption had become a perceived necessary start to each day in order to function normally. One participant described a situation whereby she would experience a headache when insufficient coffee had been consumed but the same participant also experienced a headache when she had consumed more than her usual intake.

'I could do that [drink more coffee], but I do find that then I can't sleep. I know my limitations for coffee. I know when I've had enough. If I don't have coffee I get a headache. If I have too much coffee I get a headache.' [Participant D, Female, 35-44]

The same participant also experienced some increased awareness of her heart rate when she had consumed a lot of coffee:

'I do find though, on those days, if I have three or four [coffee pod brand] at home, I normally do have a minimum of three, I am quite buzzy, so I tend not to drink coffee until the six, seven, eight o'clock treat from [branded coffee shop], I drink nothing from the morning ones. If I have a lot caffeine I do get a bit palpitationy [sic], only because my coffee's so strong.' [Participant D, Female, 35-44]

One participant found considerable physical disbenefit from coffee since it had always made her vomit.

'When I first started work, people make coffee in the morning, tea in the afternoon. I got presented with it. Though, on the list, it said I only drank tea, someone had made me coffee, and didn't realise. I took a nice big mouthful, and, ah! It makes me sick.' [Participant G, Female, 55-64]

4.4.2.3 Opportunity - physical and situational circumstances which must exist in order for coffee drinking to be possible

Opportunity is an overarching theme and refers to the physical and situational circumstances, such as location, work, and time, which must exist in order to make coffee drinking possible. For example many participants cited work related reasons for coffee not being consumed during the working day due to being impractical, inappropriate, or having insufficient breaks. Work also affected the opportunity for some coffee preparation methods. For example one participant described an enjoyment of filter coffee on weekend days away from work, whereas on days when she was at work the only option was for coffee from a vending machine.

'Probably weekends I drink more because I've got use of the machine over the weekend, so I would make up a machine, a filter coffee, fill the machine and do

that a couple of times, so...and then I can drink as much as I want as and when I want, rather than restrictions at work.' [Participant M, Female, 55-64]

Contrary to this, another participant who worked in the restaurant industry described access to an espresso machine in this setting and this had become part of their *baseline regular intake* on working days.

And another participant had access to a branded coffee shop that was available in their workplace:

'Sometimes, because there's [branded coffee shop]… I will often have a latte or a flat white at work.' [Participant L, Male, 35-44]

Location was another area related to opportunity of coffee intake. Home was generally the setting for much of the coffee intake in participant's *baseline regular intake* whereas away from home, opportunity tended to influence the *opportunistic variable intake*. Interviewees provided examples of this opportunistic intake in visiting other people's homes, whilst shopping, and after meals in restaurants.

'A cappuccino. Sometimes I do have a latte. If we go out for a lunch - because we go to a favourite pub of ours, for lunch, sometimes - I'll have a latte then, because they do make a nice one.' [Participant C, Male, 65-74]

Time was another factor related to opportunity. Insufficient time was a factor related to restricted coffee intake, or affected choice of preparation type and size of cup. In this context time affected how long it might take to prepare and how long it might take to drink a particular cup of coffee.

'No. I was too busy to drink coffee yesterday' [Participant B, Male, 25-34]

'No. It's just fitting it into the timescale, what time I got up, what time I was having breaks and things like that really and where I was.' [Participant M, Female, 55-64]

Other people could also affect opportunity for intake. For example some participants described their intake varied depending on whether they were offered a cup of coffee by a partner at home or a work colleague, especially those in which making coffee themselves was seen as an effort:

'Oh yes. I would have thought so. I'm a bit lazy if I'm honest in making my own teas and coffee. [laughter] If my wife says do you want a cup of tea love I'll say 'oh yes please'. Other than that I won't bother myself. I'm a very lazy person that way.' [Participant A, Male, 65-74]

For other, partners could provide a non-instant variety:

'It does, so my wife generally gets fairly freshly prepared coffee beans. Freshly cooked, or whatever they are, and then buys in a packet every couple of weeks, maximum. The coffee roaster is freshly roasted that week, and then she grinds it as we use it, so actually it's quite fresh coffee. That's, apparently, the best, and it definitely is nicer, at home.' [Participant N, Male, 55-64]

4.4.2.3.1 Creating opportunity

Creating opportunity refers to data where participants had suggested methods that they could use to create opportunity to drink more coffee and to overcome lack of opportunity identified in their daily lives. This was in response to being directly asked about increasing coffee intake and was included in the topic guide. For most participants, opportunity was not a significant barrier to increasing coffee consumption in their daily lives and, as

described previously, capacity could simply be created by substitution. For others, opportunity could be created by innovations as simple as putting in extra drinks breaks:

> *'I'd say it'd be fairly easy. I mean in my daily life when I'm working, I'd just think well, 11 o'clock I'll have a little bit of a [coffee] break, and three o'clock I'll have a little bit of a [coffee] break.' [Participant O, Male, 55-64]*

4.4.2.4 Flexibility – adaptability in coffee drinking behaviour

Flexibility is an overarching theme that refers to evidence in the data for adaptability in the coffee drinking behaviour of a participant that would purposefully overcome the automatic, or routinised drivers of coffee intake to allow changes in consumption, whether towards drinking more or less coffee.

4.4.2.5 Demonstrates flexibility

Participants varied in how flexible they were in any deviation from their *baseline regular intake*.

> *'If I felt that um, through professional help like yourself that you said to me we don't think there is any harm in you having a few extra cups of coffee then I'm quite happy to do so, but if someone saying, I might have misunderstood that lady, its best that you come off it, well she didn't tell me to come off it, but don't drink so much of it, I thought I might as well come off it altogether, so that's what I've done.' [Participant A, Male, 65-74]*

> *'No, it's not like a get up in the morning and think, oh, I've got to have a coffee, which some people do. No, I can take it or leave it, really. I'll have tea or - you*

know. I sort of grew up drinking tea, really. Being a builder, as well, you've got to drink tea.' [Participant E, Male, 45-54]

Some participants expressed adaptability in imagining drinking two extra cups of coffee each day and how they would create capacity and opportunity to achieve this. Some participant responses suggested flexibility linked to which preparation types, or size, might be most beneficial to help liver health:

'Yes. No, that would be palatable, and if there was [advice to] actually drink it in a slightly different way, or a different type of coffee, again I would be open to that. For example, where we have our freshly ground coffee, it's probably, on balance, going to be better for you, if anything is good for you, than instant. Generally, all foods would be the same. I guess, if you said, 'Drink that as an espresso,' or something, I would probably do that.' [Participant N, Male, 55-64]

'Yes, I mean personally I'd probably, yes. If it's just a number of cups of coffee, then I'll just have the instant stuff that we have, but on the other hand if there is some specific quantity of stuff, then it'd need to be a bit more scientifically measured.' [Participant O, Male 55-64]

Brand was also a factor that could influence flexibility:

'Pretty decent. Better than [branded coffee shop] Oops. Um, yeah if I'm out and about it town preferably I'd avoid [branded coffee shop] because I don't particularly like [branded coffee shop], but yeah, no, literally wherever is about. I'll go and get a cup of coffee from there, I'm not too picky but, preferably [branded coffee shop] is my favourite brand.' [Participant B, Male, 25-34]

4.4.2.6 Demonstrates inflexibility

Some participants expressed much less flexibility in deviation from their *baseline regular intake*.

"It's completely different. If someone gives me a cheap, horrific coffee…even if I have to have a headache and go without for the rest of the day, I won't drink it. If I forget my coffee I don't drink work's because it's horrific, so, yes, coffee snob." [Participant D, Female, 35-44]

"No I wouldn't drink nothing different. It would be just the same.' [Participant A, Male, 65-74]"

4.4.2.7 Future Research – acceptability and design of the proposed future research

Future research is an overarching theme that refers to aspects of acceptability and design of a proposed future randomised controlled trial in which increasing coffee intake would be tested as a treatment in NAFLD. Data related to the future research were specifically driven by questions within the structured topic guide.

4.4.2.7.1 Acceptability

Acceptability encompasses the intervention for drinking more coffee, randomisation between more coffee and usual coffee, and additional blood tests and scans that would be a necessary part of the research. There was universal acceptance for the concept of the proposed intervention as described by the interviewer during the interview. Indeed, the proposed study was almost construed as inconsequential especially in light of the potential benefits to liver health:

'I don't think there is anything wrong with [asking people to drink more coffee], at all, to be honest with you - its not like you are asking someone to cut their arm off, um, …Um. Yeah. I don't think that's bad.' [Participant B, Male, 25-34]

'It's hardly a big ask, is it?! When you've got 16 hours when you're awake, I'm sure during that 16 hours you can actually fit in an extra couple of cups of coffee.' [Participant O, Male, 65-74]

Some participants expressed ideas about how the impact of asking people to drink two extra cups of coffee a day might be different depending on baseline intake:

'I would have thought that was quite acceptable and reasonable. It's not as if someone's saying you've got to have half a jar of coffee. I would think a lot of coffee drinkers drink at least two cups of coffee a day. I know they do in the office. No, I would have thought that would be a reasonable level, to go from nothing to two. If it's somebody that's already drinking it, it's going to be extra, so it would be dependent on how much they were already consuming.' [Participant G, Female, 55-64]

Some participants saw randomisation as an integral part of the research method:

'Yes, if you agree to go into a trial you could be - It's like if you go to trial on a drug, it makes no difference, you could be given a dummy tablet or the tablet that works, either way you're not going to know. So, I think it's fine. If you agree to go into a research situation then you are agreeing to either go one or the other side of the research, aren't you? So, if you sign up to agree to it, no matter which one you're in, you're in. If I agree to do a research, I would assume that I get put on either the trial…' [Participant D, Female, 35-44]

Other participants did not appear to fully understand the purpose of the randomisation aspect of recruitment and instead suggested influencing allocation:

'*Thirty people, and you've looked at their notes, you know, you could look at mine and say, 'Would the extra caffeine affect his blood pressure tablets? We'll put him*

in that group', or, 'We could put him in the extra two cups of coffee group, because it doesn't affect him at night; it doesn't keep him awake.' If you're interviewing someone and they said, 'Oh, I can't drink coffee after three o'clock because it keeps me awake', then would you make them try and fit an extra two cups of coffee in during the day? …' [Participant E, Male, 45-54]

Others took the idea of randomisation a step further and suggested a stratified approach to ensure non-coffee drinkers ended up in both arms:

'Yes, but we're talking about randomisation. To a certain degree, if you've got two that are similar - two non-coffee drinkers - to have one in each is far better than to randomly pick names out of a hat, and have the non-coffee drinkers in the not-having-coffee.' [Participant G, Female, 55-64]

Tests were near universally seen as acceptable, if not essential to the research method, participants highlighting that without such elements the research would not reach its objectives. However, all components of a future research study must be laid out in full at the beginning of the study as acceptance hinged on alignment with expectations:

'As long as everybody agrees. As long as before the tests start, its all laid out on the table, right, this is what needs to be done this is what we'd like to do and this is the path we'd like to take….I think if you got half way through the tests and then by the way we want you to do several blood tests I think that would be a bit unfair.' [Participant B, Male, 25-34]

Part of this included a clear rationale for conducting the research. One participant had previously been in a trial of fish oils and had found some of the testing a burden:

'You had to take a tablet every day - whether it was the real one or placebo - I don't think you ever get to find out. The thing that put me off this, initially, when I was asked about this was, with the fish oil one, the amount of testing, it seemed to

go on for days and days. That's the thing that would put me off. I guess the other thing is, I'd want to be convinced. I'd want to see the rationale for even trying this.' [Participant P, Male, 35-44]

Some form of compensation for any costs associated with attending the hospital for tests was also raised as an important consideration:

'Yes, you'd probably have to, if they're coming in here for scans, pay their parking, but blood tests, sometimes you can get them done at your GP. If you've got to come here, if there's a cost like that, you might have to offer to offset that.' [Participant G, Female, 55-64]

Others were keen to highlight that waiting around in hospitals for scans and blood tests could be a lengthy process and therefore should be minimised in frequency:

'Yes, if it's pretty quick. If it's a scan or a blood test, you can do that in less than an hour, right …There seemed to be lots and lots and lots of tests. Yes. If it was an hour - well, it's never an hour, is it? For me, for example, it's an hour to get back and forth to the hospital, but if it was a couple of hours every six months, that would seem probably reasonable.' [Participant P, Male, 34-44]

4.4.2.7.2 Design of a future study

Preferences for what the extra two cups of coffee a day should comprise within a research project was a feature of the structured topic guide. Participants varied in thoughts about whether the coffee should be funded by the research that would allow participants to drink more of their preferred coffee type:

'I think if it's coffee at home if they're drinking their own instant coffee then I don't think you should have to subsidise that really, because its only a couple of spoons isn't it, but I think if all they're drinking is blooming high street coffee which is like

four of five quid a pop, then yeah, if you're asking people to drink more of that, I would imagine that it would only be fair to subsidise it. Not necessarily give it to them free but say right you're getting the enjoyment of drinking it and we're getting the results so we'll meet you 50:50 somewhere.' [Participant B, Male, 25-34]

'I buy very expensive coffee. So, if I had to drink another two or three cups a day, then that coffee I'd have to buy two lots a week which would probably cost me £10, if not more. Whereas now I probably only pay about £7 a week. So, yes, it would be like another £5 a week, because I'd be adding two cups of coffee. Bearing in mind I can drink three to five anyway. If it was [coffee pod brand] however, that would be £20 a week.' [Participant D, Female, 35-44]

'Yes. If you said to me you wanted me to drink an American coffee from the [branded coffee shop], sort of thing, and you wanted me to drink two of them a day, 1) I'd have to get to a [branded coffee shop], anyway.., then I would say, yes, I think you should be paying for that, because it's something that you want us to try, and it's something totally out of the norm. Yes, I would probably say I think you should chip in for that, yes.'[Participant I, Male, 55-64]

Some participants suggested no additional financing would be necessary for additional coffee consumption, but these were generally those not drinking more expensive coffee types within their *baseline regular intake*:

'If you wanted me to drink my own brand, then I'd have no problem at all doing it myself. I wouldn't expect you to pay for that, but, if you wanted me to drink some fandango kind of coffee, then I'd say, 'Well, that's not my normal sort of thing', so, perhaps you shouldn't jump on to that sort of thing, but, yes, for my own brand, I've got no problem at all. I wouldn't even think about asking for money for that' [Participant I, Male, 55-64]

If coffee was going to be supplied by the research team and if this was instant coffee then the type of instant coffee used was going to be important, and giving an unbranded coffee might not help:

> *'Yes, I'd be happy as long as it was a decent brand. If you gave me normal [coffee brand] freeze-dried, you'd get it back. If it was [instant coffee with ground coffee blend brand] or [instant coffee with ground coffee blend brand] or [instant coffee with ground coffee blend brand] or something like that, then I'd take it.' [Participant D, Female, 35-44]*
> *'What if you didn't know what the brand was?'[Interviewer]*
> *'I'd know.'*
> *'Would you drink an unbranded coffee?*
> *'If I drank it, I'd know if it was cheap.*
> *'Would you drink it?*
> *'No*.'

> '*If you said to me, 'Right, drink an extra two cups of instant coffee', that wouldn't appeal to me so much, because, obviously, I'm used to drinking - I would most probably do it for the survey, most probably, but it wouldn't be something to think, ooh, yes, I'll go home and have one of those instant coffees', ... I don't know if you drink coffee, but you know what an instant one and a nice one taste like. I don't know; tough one.' [Participant E, Male, 45-54]*

If the coffee was to be supplied to participants for the duration of the research it was generally seen as very important that the coffee tasted good. For non-instant coffee drinkers the idea of instant coffee being supplied was not appealing. Some participants would not wish to be involved if it meant drinking instant coffee, whether it was supplied by the research team, or given funds to purchase their own:

> *'I don't know what is in the instant coffee, for example. With [coffee pod brand] they're quite prescriptive in telling you how much caffeine they estimate is in each pod…They kind of tell you what each pod has in it. They're much shorter and*

stronger, I think only a certain kind of person drinks that. I think the vast majority of people, from what I can see, are quite happy to drink [instant coffee brand], instant coffee. Whereas for someone like me, I wouldn't drink instant coffee at all.' [Participant L, Male, 35-44]
'You wouldn't want to be either asked to drink instant or given instant to take?' [Interviewer]
'I would have dropped from your study, I can't drink it to be honest, I don't like the taste of it at all.'

Some however would be willing to try to drink the instant coffee in a study but would not continue to drink it if the taste was not pleasant:

'I like nice coffee, so if it was something they wanted me to drink to see it helped with their study then I would give it a go, but if I didn't like it I'm afraid I would have to say, 'I don't like [laughs] this coffee and I'm not going to be able to drink it!' [Participant M, Female, 55-64]

Instant coffee was also seen as convenient whereas non-instant preparation types could add a tier of preparation complexity for people:

'I've got to be careful how I say things, I suppose, but there's a lot of people out there that, everything is instant for a reason. Whereas, again, if you were to say to me, 'Look, this could be beneficial, would you mind trying it?', then why wouldn't I, if it's for my benefit as well. I can't answer for any other people, but I would think that the majority of people - no, that's not even fair to say that - but, I'm sure there would be a lot of people out there that wouldn't want to do that, because it would be changing something that's very easy into something more difficult.' [Participant I, Male, 55-64]

Robustness of the scientific method were described as reasons for participants who thought coffee should be supplied because the amount of coffee consumed could be

more easily standardised. Some participants raised this approach as more akin to taking a medicine. Standardising a cup size for the research was also seen as important:

> *'I think it would have to be a measured amount wouldn't it - to get an accurate, sort of like, result from something. If for example you just asked someone to have an extra two cups of coffee and one person has large coffees and one person has small coffees those results are going to vary because obviously the consumption of coffee would be different so I think in looking at results - I suppose you'd have to work out how much that person's average coffee consumption would be' [Participant B, Male, 25-34]*

4.4.2.7.3 Assistance to increase coffee consumption

The concept of additional assistance with remembering to drink the additional two cups of coffee a day within the research study was another element directly explored in the interview guide. Most participants did not think that they would need any additional assistance to remember. They expressed that drinking the extra coffee would easily be remembered and soon become part of a routine.

> *'It wouldn't be a problem to me, because I can remember to do it, but there might be some older people who might have memory problems, or something like that. I can't see it being much of a problem to many people.' [Participant C, Male, 65-74]*

Some participants did think that text message reminders might be a useful addition, whilst others felt that they already received too many messages and this would be unwelcomed. One participant suggested a specific application on their mobile telephone that would send notifications that it was time to consume a coffee. Some participants also expressed an idea that keeping a record of the coffee they had consumed each day would help them keep track of their coffee intake.

> *'I'm a great person of trying to make sure things are put down on a bit of paper or something like that. That reminds me – oh – I need that extra cup of coffee. So*

many things going on all day. People are so busy today they don't even think of things like that. If you think you've got to take an extra two cups of coffee they probably need a little nudge in the right direction to do so.' [Participant A, Male, 65-74]

The suggestion that a research nurse could telephone them to remind them to drink extra coffee was universally thought unnecessary and time or money associated with such a component of the research would be better used elsewhere.

4.5 Discussion

Seventeen semi-structured interviews were conducted to explore patterns of coffee consumption in people with NAFLD, views about drinking more coffee, and perceptions of future research in which coffee could be tested as a treatment for patients with NAFLD. Overarching themes identified from the analysis suggested that a person with NAFLD would be more likely to increase their *baseline regular intake* of coffee in everyday life, if they have the enabling capacity, motivation, opportunity and flexibility. These factors were complexly interwoven with one another, affected by the numerous subthemes identified in the analysis, and arguably would need to be aligned for behaviour change to occur.

4.5.1 Capacity

Capacity could be limited by an already substantial *baseline regular intake*, or where someone regularly reached the perceived point of having reached full capacity of coffee. However, increased capacity could be created by substitution, such as replacing any habitual cups of tea or cola with coffee, and evidence suggested that people already did this, or expressed this as a way to achieve increased coffee consumption in their life, when directly asked. Since most participants consumed a number of cups of tea or cola on a daily basis, substitution for coffee would offer a practical way of increasing daily coffee consumption and would be especially useful in people with unpleasant physical effects from total caffeine or fluid volume, such as insomnia, or frequent urination.

4.5.2 Motivation

Motivation could be influenced by a number of push and pull factors such as a coffee ritual, in which the *baseline regular intake* was embedded, preparation type, taste, brand, financial cost, effort, reward, beliefs about coffee and health, health professional advice, and physical benefit or disbenefit. Belief that coffee would be good for the health of the liver seemed to be a strong, albeit hypothetical, motivating factor, and in this situation, all three non-coffee drinkers indicated that they would start drinking coffee even though the key reason for not drinking it currently was an aversion to the taste. Even a participant who was physically sick following ingestion of coffee suggested they would attempt to overcome this by hiding coffee in food such as a chilli-con-carne. However, mixing coffee in food may affect the way the coffee compounds are absorbed and/or metabolised, may not be appropriate for all types of coffee, and may not be possible to extrapolate the findings of a randomised controlled trial to be able to recommend such a work-around.

4.5.3 Opportunity

Opportunity for drinking coffee could be influenced by time, location and other people. For example where time was limited coffee might not be consumed at all, such as in certain work situations. However, opportunity could be created to overcome barriers of time or availability, as long as motivation to drink more coffee was positioned positively.

4.5.4 Flexibility

Evidence of flexibility in terms of deviating from *baseline regular intake* suggested that a participant might be more able to increase their coffee consumption. Most participants seemed to express some degree of flexibility. This was also highlighted by participant driven ideas to work around any possible barriers that they had discussed with respect to drinking more coffee in their everyday lives. However a few participants demonstrated inflexibility in their current coffee intake and it appeared that they might not easily be able to increase coffee consumption. This tended to be driven by a requirement for a specific preparation type or brand, or when there was a perception that the current consumption was more than adequate. Arguably such inflexibility might be overcome through strong motivating factors such as knowledge that increased coffee consumption could improve or protect the health of the liver, which would be further reinforced by healthcare professional endorsement.

The relationship between *baseline regular intake*, *opportunistic variable intake*, capacity, motivation, opportunity, and flexibility is conceptually illustrated in Figure 28. *Baseline regular intake* and *opportunistic variable intake* are both shaped by capacity, motivation, opportunity and flexibility. For some people with NAFLD, *baseline regular intake* may already exceed a threshold intake for benefit to liver health, such as those consuming ≥4 cups a day, as discussed earlier in the chapter. Others may have a sub-threshold baseline regular intake (0 cups, or 1-3 cups/day) and could target a threshold intake. A future intervention to bridge this coffee intake gap should also take into account the *opportunistic variable intake* that will influence total coffee consumption.

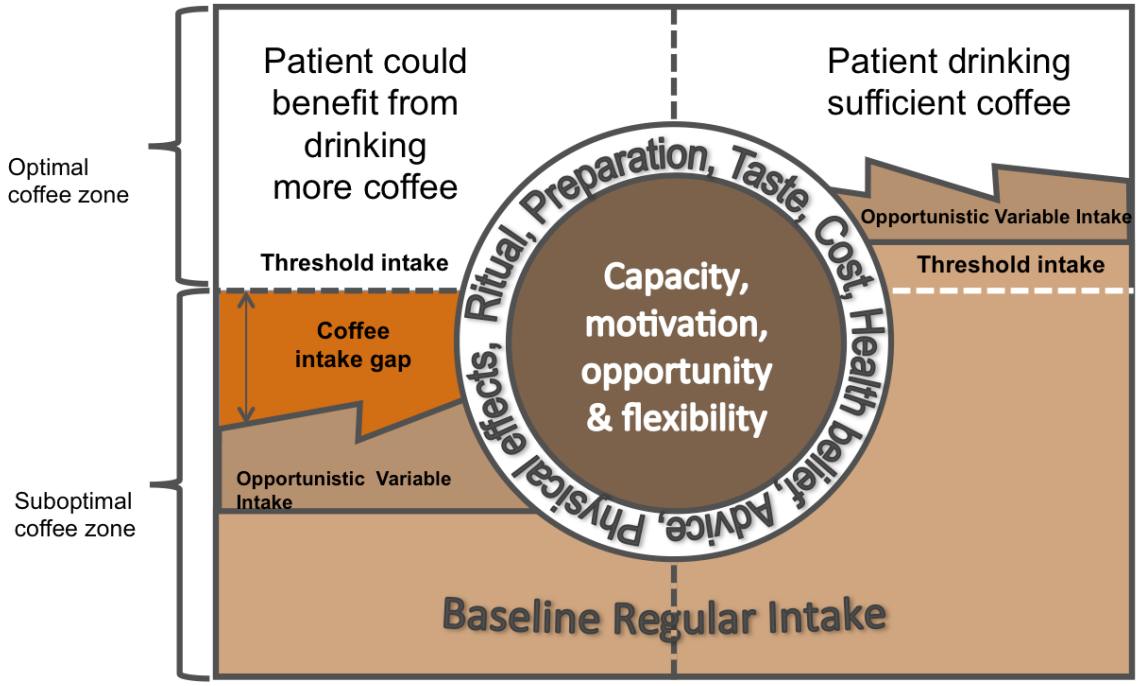


Figure 28: Conceptual relationship between baseline regular intake, opportunistic variable intake, capacity, motivation, opportunity and flexibility

Whilst there is some overlap between components of each theme, missing one of the key elements would likely result in no increase in consumption of coffee. For example if someone had apparent capacity for drinking more coffee, opportunity during the day to drink more, and were flexible in deviation from their *baseline regular intake*, but no

motivation because coffee was too expensive, then it is unlikely that they would increase consumption. Similarly, if someone had capacity, were flexible and strongly motivated to drink more due to belief in the positive health effects, or endorsement by a health care professional, but had no opportunity to consume more during the day due to work commitments, and unable to drink coffee after work due to issues of insomnia, then an increase in coffee consumption would also be jeopardised. Furthermore, a person might have motivation, opportunity, and flexibility but simply no apparent capacity because they have reached a point of perceived full capacity, then they could not achieve an increase in coffee consumption. However, behaviour change towards drinking two more cups of coffee could be enhanced by:

1. Creating capacity, for example by use of substitution
2. Enhancing motivation, for example by favourable taste and preparation experience
3. Creating opportunity, for example by planning coffee breaks in the working day
4. Enhancing flexibility, for example by making small changes to existing routines

4.5.5 Negative Case Analysis

One participant suggested that they would not have the capacity to drink more coffee. However, this participant had the highest *baseline regular intake* of all participants, drank strong varieties of coffee, and had symptoms suggestive of physical dependence of caffeine. Rather than increasing coffee consumption irrespective of baseline intake, it is likely that future health advice may be to target intake, and this participant would have likely exceeded that threshold, as described previously. However the concept of caffeine addiction and intolerance is an important one and the participants in the present study may not be representative of these issues. A larger sample would have permitted further exploration. Addiction to caffeine is further discussed in the main thesis discussion.

Whilst most current coffee drinkers felt that increasing their coffee consumption by two cups a day would be easily achievable, the reality is that they may experience caffeine related physiological effects that may make higher consumption unpleasant and unsustainable. Substitution might alleviate some of these issues and a future randomised-controlled trial would need to carefully account for total non-coffee caffeine consumption in assessing the effects directly related to changing coffee consumption.

4.5.6 Behaviour Change

Changing behaviour to increase coffee consumption would likely be subject to the same challenges facing other lifestyle changes, such as increasing the consumption of fruits and vegetables, or reducing the intake of alcohol. In this context, and in the hypothetical situation that experimental evidence existed that increasing coffee intake was beneficial for liver health (for example, following the proposed randomised controlled trial) then healthcare professionals might be able to adopt lifestyle change evidence-based techniques such as healthy conversations[272], motivational interviewing[273] or brief interventions[274] to help elicit change.

The COM-B model[268] for behaviour change helped to inform the design of the topic guide used in the interviews, and it is therefore not surprising that the present research identified overarching themes of capacity, opportunity, and motivation, that align almost directly with COM-B (Figure 29). Whilst our themes of opportunity and motivation have equivalent definitions as the COM-B model, our 'capacity' differs slightly from 'capability'. The name 'capacity' was felt to have a more appropriate meaning, commonly defined as 'the maximum amount that something can contain', and in this sense is more directly applicable to coffee consumption, and some of the issues related to feeling full to capacity and being unable to physically drink any more. Our theme of flexibility does not feature explicitly in the COM-B model but is likely embedded in the automatic sub-classification of motivation that includes habit formation. Flexibility means disrupting such habits and many other factors can contribute to an individual's willingness for habits to be changed, requiring energy and time.

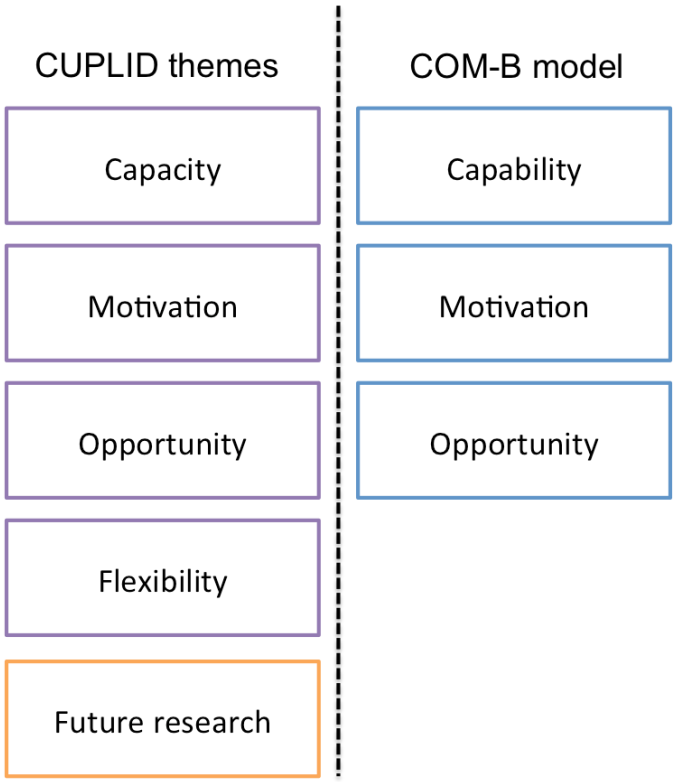


Figure 29: CUPLID theme alignment with the COM-B model

4.5.7 Future research study

The concept of a research study in which coffee is tested as a treatment to see if it could reduce the risk of progression was universally seen as acceptable by participants, including both current coffee and non-coffee drinkers. Set in a context of potential health benefits, increased coffee consumption was construed as almost inconsequential to participants, with it being described as both acceptable and feasible. By contrast having tests such as blood analysis and scans were described as more likely to be inconvenient, repetitious, time consuming, and potentially have a financial impact, such as with car parking fees in hospitals. Related to this, participants emphasised the necessity of procedural transparency from the outset of study recruitment, such that every potential participant would know what was expected of them throughout the research process. The concept of randomisation was understandably more difficult for some participants to grasp, but was also generally seen as acceptable.

Participants also discussed the financial implications of the coffee intervention. Many participants had a strong preference for specific preparation types or brands of coffee, and

drinking more of their preferred type was generally felt as the preferred option. However, for those whose *baseline regular intake* consisted of drinking mainly non-instant coffee, the additional financial impact of this was of concern, and an allowance provided by the study was seen as an appropriate compensation. Participants whose *baseline regular intake* consisted of mainly instant coffee perceived financial compensation for extra consumption unnecessary. This highlights the relatively inexpensive nature of some types of instant coffee, where as previously discussed in chapter 3, a jar of instant coffee can cost the same price as a single coffee purchased from a branded high street coffee shop.

Linked to strong preference for taste or preparation method, non-instant coffee drinkers were divided as to whether they would entertain the idea of trying to drink instant coffee for the benefit of the research process. Those that suggested they were willing to give it a go also said they would be quick to stop if the coffee tasted unpleasant, and would be quick to let the research team know.

Acceptable approaches to the nature of the intervention within a future randomised controlled trial require the results from the larger, more generalised sample, obtained in the quantitative phase of the survey (chapter 5). Indeed, findings clearly signal that the precise nature of the coffee intervention is likely to be incredibly important to levels of participation.

Another important aspect of the intervention in a research study is whether additional support or reminders need to be provided in order to help participants adhere to the intervention. Most participants did not feel they needed very much help in order to remember to drink two extra cups of coffee a day, either as part of everyday life, or in the context of such a study. Some felt that a reminder via a text message, or some type of reminder from their mobile phone, might help establish routine. Specifically more intensive reminders such as a telephone call from a research nurse were not seen as necessary or cost-effective.

The qualitative phase of the mixed methods study was also used to improve the design of the questionnaire for the survey phase. This was planned as part of the sequential exploratory mixed method design and discussed further in the next chapter.

4.5.8 Strengths and Limitations

The design of the qualitative phase of the mixed methods study, and specifically the use of semi-structured interviews and thematic analysis, was an appropriate methodology to achieve the research objectives as described previously. The approach allowed sufficient data to be obtained to address the research question and inform further development of the questionnaire to be used in the survey phase. This pragmatic approach also gave scope for unanticipated ideas to develop during the interviews that might not have been possible with a fully structured interview process, or with a purely quantitative approach. Using the COM-B model to inform design of the topic guide also ensured data could be collected that was directly relevant to behaviour change, and therefore important to future intervention design, a key strength of the COM-B model.

A further strength of the present study included the use of a codebook, which included code descriptions and exemplar text, which was produced and developed in conjunction with a second coder for the first five interviews. The second coder was a professor of qualitative research, and also co-supervised the author throughout the qualitative phase of the mixed methods study. The codebook helped to ensure consistency in data extraction over the entire dataset, and the multiple coding for part of the dataset was a useful way to ensure a thorough approach. Candidate themes were also discussed and refined throughout the study during regular supervision meetings.

The sample was a purposive sample of patients with NAFLD attending a liver outpatient clinic in one NHS site. Recruitment challenges meant that the maximum variation matrix was not fully completed because insufficient time was available to wait for participants with specific characteristics within the matrix to be recruited. As such there were less female and less non-coffee drinking participants than anticipated. However, the proportion of 18% non-coffee drinkers was only slightly lower than the general population proportion of 22% non-coffee drinkers in the UK Biobank cohort[275]. Whilst criteria for data saturation were met, this may have only been true for current coffee drinkers, rather than non-coffee drinkers. It is possible that the idea of taking part in an interview about coffee was less appealing to people who do not drink any at all, especially if they associate coffee with an unpleasant taste. However, despite low numbers, valuable data was collected from this important group of non-coffee drinkers who potentially have the most to gain by introducing coffee into their diet in the hypothetical situation in which coffee has proven benefit in NAFLD.

NAFLD is more prevalent amongst males compared to females[276] although the difference in proportion is not as extreme as in our qualitative sample. It is not possible to know the characteristics of people who were approached by the existing clinical care team and declined to take part. Whilst generalisability, in a population sense, is not an intention in qualitative research, it is likely that the findings in this study would be similar in people with NAFLD in other UK populations since coffee is so engrained within the culture of a country[261] and it is likely that coffee drinking patterns would be similar. However in other countries, with a different coffee drinking culture, patterns of coffee intake are likely to be different, as may be perceptions of coffee and health. The UK is fairly unique in the high proportion of coffee consumed as instant coffee. This instant coffee culture may be starting to shift as modern espresso-based coffee preparation types become increasingly popular, both in the home and out of home sector, as well as the surge of coffee pod and capsule machines for domestic use over recent years. Data highlighted in chapter 3, suggest that nearly 75% of all coffee consumed is still instant and 78% of UK coffee drinkers still regularly consume it. However, the findings of the present research appear to have strong conceptual transferability when considering key findings regarding participants views on likely barriers and enablers to increasing coffee intake, and factors identified within the COM-B model are likely to hold in other populations and contexts.

A further limitation is that the semi-structured interviews were at risk from response bias. Specifically, all three non-coffee drinkers suggested they would introduce coffee into their diets if it were beneficial for their liver health. This was despite all three disliking the taste of coffee. The positive response to the idea of introducing coffee may therefore have been partially driven by a desire to be agreeable with the interviewer. However, the benefit of the qualitative approach was the richness of the data, and the analysis permitted vertical (intra-case) and horizontal (inter-case/comparative) analysis, which was sensitive to any contradictions within individual narratives as well as allowing interrogation of the meaning within the narrative accounts. Specifically, meaningful accounts of participants weighing the pros and cons of coffee intake, including the potential health benefit, which in the end, outweighed aversion due to taste, alleviate some suspicion regarding response bias. Including a greater number of non-coffee drinkers would have allowed a deeper understanding of variation in views with regard to the issue of taste versus health benefit. The quantitative phase of the research, although not free from risk of response bias, may provide further insights.

4.6 Conclusion

Seventeen people with NAFLD were interviewed to explore patterns of coffee consumption, views about drinking more coffee, and opinion on a future experimental study in which coffee is tested as a treatment in fatty liver disease. Most participants felt they had capacity to drink an extra two cups of coffee a day with no additional help required. The proposed intervention of drinking two additional cups of coffee each day was considered very acceptable, including among those currently drinking no coffee, as were tests needed as part of the research, as long as study expectations and the rationale of the study were laid out fully in advance. There was mixed opinion as to whether the additional two cups of coffee should be supplied or funded, and this appeared to be an important factor influencing whether people would be willing to take part. The survey phase of the mixed methods study was designed using insights from this qualitative study and allows us to further test and explore the same questions in a larger sample of people with NAFLD. This will be important to enhance the design of an intervention in a future randomised controlled trial.

4.7 Reflexivity

I was aware as I began to design this phase of the mixed methods study that there was a key question to answer, which was whether we should proceed with a proposed randomised controlled trial. Specifically, if people with NAFLD would not feel able to drink any more coffee than they already drink then conceptually an intervention of drinking more coffee compared to usual coffee was never going to work, and even if coffee had proven benefit in reducing the risk of progression along the pathological pathway of NAFLD, people may simply be unable to drink more in their everyday lives. However, I did not wish to rule out the benefits of novel ideas being identified in the research process and to understand the nuances of individual participants relationship with coffee, the qualitative approach felt justifiable, especially to understand subtleties in their response. I was also aware that I had quite a utilitarian purpose for the research, and indeed quite a utilitarian mind set, and needed specific topics addressed to answer my research questions. As such, the philosophical approach of pragmatism allowing for non-relativist positive action meant that I could achieve my research objectives, and using the COM-B model of

behaviour change in planning the topic guide further re-assured me that I would achieve my objectives.

The design of the protocol took a while to finalise but was definitely worth the significant time investment and included creating all the necessary documents such as the topic guide. As recruitment began I was very aware that the coffee study was low down on the list of task priorities for the existing clinical team during busy clinics. Clinicians, especially middle-grade doctors, differed from one week to the next. However, over a number of weeks their faces became familiar, as did my own. I would linger in the corridor by the clinic and try to give them the recruitment packs face to face to remind them of the study and that I was around should they find suitable patients whom may be interested in taking part. It was my suspicion that sometimes they would forget to offer the opportunity to suitable patients, or perhaps make a judgement as to whether a particular patient would be suitable to be interviewed or not. One consultant admitted that they had forgotten to raise the opportunity with patients when I talked with them at the end of one clinic. As such recruitment felt like a much slower process than desired with many clinics where no one was recruited at all. However, I felt to push for a greater number of referrals from clinicians would have been detrimental to the good will I had built with the hepatology team. Furthermore, I felt strongly that the priority for all patients attending the hepatology clinic was their clinical assessment and management, and research objectives should always be a secondary consideration.

In the introduction with potential participants I explained that I was a public health doctor conducting research into coffee and liver health, and I also explained that I had a clinical background to re-assure participants that I would understand their liver condition if they wished to talk about it during the interviews. It is possible that my conduct of the interviews could lead to some response bias, perhaps giving answers that they thought I might wish to hear, especially as they knew this was my own research project, and was quite clear that I had a favourable view upon coffee in liver health, despite causative benefit yet to be determined. This may have been true of the non-coffee drinkers, all three of which agreed they would start drinking coffee if it was good for their liver health. The reality of persevering through an unpleasant taste experience may be extremely challenging. For people already drinking small volumes of coffee, increasing coffee consumption would probably be very much easier, since they were already invested in the enjoyment of the taste. I felt particularly excited when I held interviews with participants who did not drink any coffee as my curiosity was heightened as to why they did not drink

coffee and what they thought about changing this behaviour if coffee was found to be beneficial. It is possible that I communicated this excitement in a non-verbal manner and this could have contributed to some response bias.

However, the topic guide had been constructed around open-ended questions, and before each interview I reminded participants that there was no such thing as a 'right answer' in any of the discussions. Additionally the topics within the topic guide for this research were unlikely to evoke an adverse emotional response and are objectively uncontroversial, and as such, responses are more likely to represent genuine views compared to more sensitive subject matter in other qualitative research.

During data collection I also adapted the topic guide by removing the question about food containing coffee/caffeine, and medication containing caffeine, as neither seem to generate any seemingly useful data. Consumption of an 'occasional Tiramisu' was mentioned by one participant, but after reflection you would have to eat an awful lot to contribute significant caffeine into the diet, including chocolate, and so I dropped the topics so that focus could remain firmly on coffee consumption.

As interviews progressed three things became apparent. Firstly launching into the questions about current general and liver health felt somewhat awkward in the context of the research being focused on coffee. It felt like 'Would you like to take part in an interview about coffee?' and then 'Okay, so tell me about your health'! It therefore made good sense to switch the order of the topic guide so that the first discussion related to the research subject of coffee consumption and once a rapport had built up, the topics flowed more naturally into those objectively more personal in nature.

Secondly, I became aware as I conducted more and more interviews that I was able to use the topic guide less, and focus more on communicating with the participant and allowing novel ideas to come out of the interviews. Extract from the reflexive journal:

> *'I think I may be slightly improving at the extrapolation of the topic guide to probe deeper with respect to certain questions. It feels like the interviews are becoming less linear. Although themes are starting to emerge, so too are novel view points in each interview.' [Field notes entry after 6 interviews]*

Thirdly, a key change followed discussion with my qualitative supervisor who had made observations when listening to some of the audio-recordings. I had not realised that in topics related to the future research acceptability, design and assistance, I was often raising the topic in such a way that the participant would give me ideas about what they thought people in general would find acceptable, rather than what they personally would find acceptable, although clearly their own views may be contained within such projections. When I changed the way I explored these areas with participants it felt more precise, and interviews were also significantly shorter in time, although at the back of my mind I wondered whether the emphasis on what the individual would find acceptable meant that they may be driven further into a cul-de-sac of responses biased towards the favourable.

Another observation from the reflexive journal was how participants appeared when talking:

> *'It almost feels like coffee drinkers' eyes light up when they talk about drinking coffee. This could have many reasons behind it such as the pure joy of taste, the social aspect, the fact that coffee equates to a break, a treat etc'*
>
> *[Field notes entry after 8 interviews]*

It is difficult to know the value of such non-verbal cues. It is possible that this indicates that the coffee-drinking participants who had agreed to take part were particularly invested in coffee drinking and it is possible that their responses may be different from those whose eyes do not light up when talking about coffee drinking, presumably such as those not interested in taking part in the study. The survey of a more representative sample of people with NAFLD should help address this issue (chapter 5).

Chapter 5: Quantitative phase of the mixed methods study - Exploring coffee consumption in people with non-alcoholic fatty liver disease and understanding barriers and enablers to increasing their intake (CUPLID)

5.2 Background

The background to the sequential explorative mixed methods study, including objectives of the research, was detailed at the beginning of the previous chapter. The quantitative, second phase, of the study, detailed in this chapter, was informed by the qualitative, first phase. This phase consisted of the final development and use of a survey instrument to investigate coffee drinking patterns, views about increasing coffee, and acceptability of aspects of our proposed future randomised controlled trial, in a larger, more representative sample of people with NAFLD, by conducting a cross-sectional survey.

Key outcomes of the survey relevant to the research question:

- Patterns of coffee drinking (number of cups, size, preparation method, location, additional ingredients) in a representative sample of NAFLD patients
- The proportion of participants in each of three intake groups (0 cups/day, 1-3 cups/day, ≥4 cups/day)
- Summary statistics for a range of coffee consumption variables
- Summary statistics for a range of variables related to increasing coffee consumption
- Summary statistics for a range of variables related to acceptability of coffee research
- Comparisons between groups to test specific hypotheses:
    - Non-coffee drinkers will be less likely than coffee drinkers to agree to the achievability of drinking two extra cups of coffee each day
    - Non-coffee drinkers will be less likely than coffee drinkers to be interested in taking part in a future research trial in which coffee is given as an intervention
- Proportion of survey participants with misclassification between reported cups and coffee unit standardised cups

5.3 Methods

The method for the survey phase of the mixed methods study is summarised in Figure 30

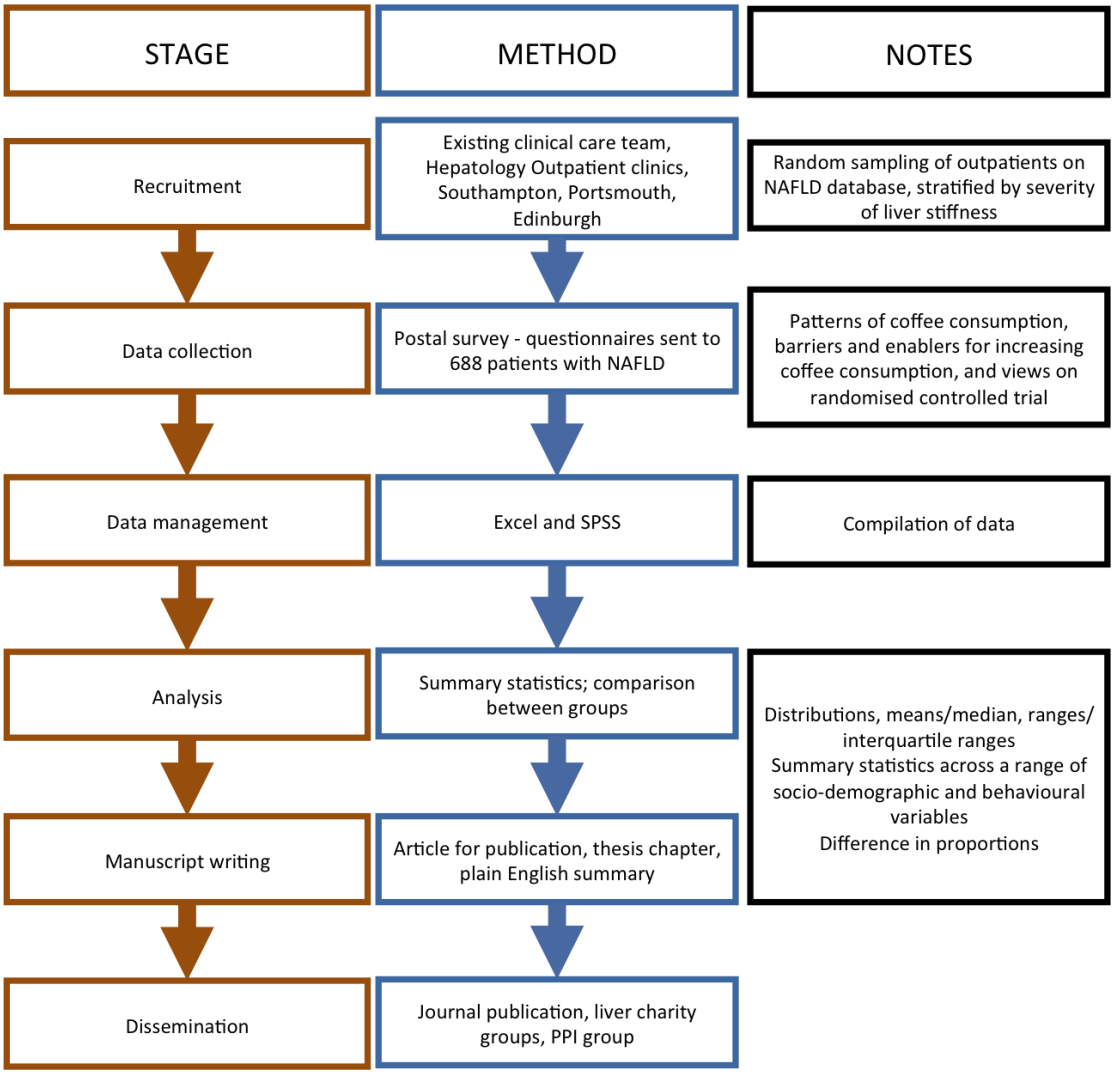


Figure 30: Quantitative phase methodology

5.3.1 Quantitative Data Collection

5.3.1.1 Creation and validation of the survey instrument

A questionnaire was used to investigate similar phenomena as the qualitative research using the qualitative findings to inform the final content of the questionnaire. The explorative sequential methodology was used to enhance the breadth (diversity of choice options), depth (range specified within an option) and structure (language content) of the final questions. The survey allowed coffee consumption to be robustly quantified in a larger, representative, population of people with NAFLD.

The questionnaire was initially constructed by RP, face validated with colleagues, and submitted as part of the original application for ethical approval of the mixed methods study, with appreciation that the final design would be further informed by a) the qualitative phase of the mixed methods study and b) 'think aloud' testing with patients with NAFLD. The qualitative phase resulted in mainly redaction and simplification of the questionnaire. The 'think aloud' technique[277] was then used with two patients with NAFLD. This technique involved RP observing participants as they attempted to complete the questionnaire and the participants encouraged to speak out loud as they read, contemplated, and completed their responses. Specific questions were asked by RP to understand how the participants were answering the questions. The think-aloud process resulted in two further changes to the questionnaire; further simplification and clarity of the part of the questionnaire used to capture coffee consumption data, and the addition of differentiation between weekday (or working) and weekend (or non-working) days.

The final survey instrument was split into seven sections. The first section asked questions about regular coffee intake, defined as at least once a week, and included a sub-section on coffee consumed the day before completing the questionnaire. Sections two through four asked similar questions about tea, cola and energy drink consumption. These non-coffee caffeine containing beverages were included in the questionnaire in order to provide insight into total caffeine intake but did include the same level of detail, and specifically did not include day before intake. This was designed as such in order to keep the questionnaire shorter and quicker for participants to complete. Section five was about participant views on coffee and health, achievability of increasing coffee consumption (caffeinated and decaffeinated), and reasons why this might not be achievable. Section six asked views about the future research, and section seven collected socio-demographic and behavioural characteristics. These included gender, age group, ethnicity, employment, house ownership, persons living in household, self-reported height and weight, self-reported diagnosis of heart disease, stroke or type II diabetes, self-reported cigarette, and self-reported alcohol consumption using an embedded AUDIT-C questionnaire. The final questionnaire can be found in appendix K.

5.3.2 Piloting of the survey

The revised questionnaire, sampling method, and creation of the postal recruitment packs, were piloted in 51 patients on an outpatient NAFLD database held by the clinical

hepatology team at University Hospital Southampton. The pilot was conducted to estimate response, and this informed the total number of questionnaires to be sent out in the full survey, in order to reach the necessary sample size.

The database had been previously constructed by the University Hospital Southampton hepatology clinical team for purposes of future research, and consisted of only patients with a clinical diagnosis of NAFLD based on the clinical presentation, abnormality of relevant blood tests, and liver Fibroscan results, in the absence of other causes of liver pathology, such as alcohol and viral hepatitis. All patients on the NAFLD database had attended the liver outpatient clinic within the previous 12 months.

The database included characteristics such as name, date of birth, hospital number, and Fibroscan result (in units of kilopascals (KPa)). Fibroscans, described previously in chapter 1, are special types of ultrasound scan that are used as non-invasive markers to assess the degree of liver stiffness, and therefore severity of NAFLD, along the pathological pathway.

Only the existing clinical care team accessed the NAFLD database. First the database was stratified into three groups of severity by liver stiffness. These cut offs had been determined following previous discussion with clinical/research hepatology colleagues/collaborators at the University of Edinburgh, and are consistent with current evidence [278,279]:

Group 1: Liver stiffness <7 kPa (Steatosis without fibrosis, or with mild fibrosis)

Group 2: Liver stiffness ≥7 and ≤13 kPa (Moderate to severe fibrosis)

Group 3: Liver stiffness >13 kPa (Possible cirrhosis)

Within each liver stiffness group, participants were given a sequential number (n). A random number generator (www.random.org) was then used to generate a sequence of 17 random numbers from 1 to n, where n was the total number of patients within each stratified group. This was repeated to select 17 patients from each of the three liver stiffness groups, and a total of 3 x 17 = 51 patients were randomly selected from the NAFLD database.

Questionnaires were prepared for each participant. Unique identifying codes were generated by RP, added to the questionnaires, and these were provided to the clinical team to assign to each patient.

The clinical team created and held a unique CUPLID database that contained the patient identifiers and the newly assigned unique CUPLID identifiers ensuring the liver stiffness groups matched up between codes and patient groups. The research team retained only the list of CUPLID identifiers so that when the linked-anonymised questionnaires were returned it would be possible to know by a simple process of elimination which unique codes had not been returned.

The clinical team then sent out the questionnaire and cover letter to all patients that had been selected during this process. The cover letter was addressed and signed by the consultant hepatologist. Patient addresses were handwritten on envelopes as evidence suggests this improved return rates compared to printed addresses[280]. Packages containing the cover letters, questionnaires, and freepost addressed return envelopes (direct to the research team) were posted using the Royal Mail postal service. The research team had no direct access to any patient identifying information and the clinical team had no direct access to any of the returned questionnaires. Consent to participate in the study was implied by the return of a completed questionnaire.

After a period of three weeks unique identifiers from questionnaires that had not been returned were re-supplied to the clinical care team who cross-referenced with their CUPLID database and sent out reminder letters and second questionnaires to only those patients who had not returned the questionnaire.

The existing clinical care team also provided anonymised gender and age group data for the non-return CUPLID codes to allow the researchers to identify broad differences between participants and non-participants.

5.3.3 Outcome of the pilot phase

5.3.3.1 Selection of sample and production of recruitment packs

The methodology for selecting the sample, and producing the postal recruitment packs, was technically very simple for the clinical team to conduct. Two members of the clinical team had volunteered to help with the project and were able to work closely with RP to ensure adherence to the protocol, and dedicate sufficient uninterrupted time. No specific problems arose during this process.

5.3.3.2 Returned questionnaires

From the sample of 51 patients invited to participate in the study, 35 completed and returned a questionnaire equating to a return rate of 69%. There were very few obvious problems with the completion of the returned questionnaires with four participants omitting one or two questions, including one participant omitting two sides of questions, where they may have turned two pages at once by mistake.

5.3.3.3 Changes following the pilot survey

Due to the high accuracy in completion of the returned questionnaires, and the high return rate, no further change was deemed necessary in the content or design of the questionnaire. This also had the advantage that the pilot data could contribute to the full survey. Following the pilot phase, a detailed methodological procedural document was constructed and shared with the principle investigators at the other two NHS sites.

5.3.4 Ethical and regulatory considerations

The protocol for the mixed methods study and the related study documents, including the draft questionnaire, had been submitted and approved by the University of Southampton Research Ethics Committee, NHS Research Ethics Committee and the Health Research Authority. The final version of the questionnaire was also submitted as an amendment following the pilot phase. Between the original ethics application and the amendment, the UK introduced the General Data Protection Regulation (GDPR). As a result of this the University of Southampton Research Governance Office stipulated that a participant information sheet should be added to the cover letter and questionnaire, which should include details of the University data privacy policy. This was constructed, approved, and included in the subsequent substantial amendment notification to NHS Research Ethics Committee and Health Research Authority, but had not been tested as part of the pilot survey. All required ethical approvals were obtained prior to conduct of the full survey.

The full CUPLID survey procedure is summarised in Figure 31 and the full procedural document can be found in appendix H. The participant information sheet can be found in appendix J.

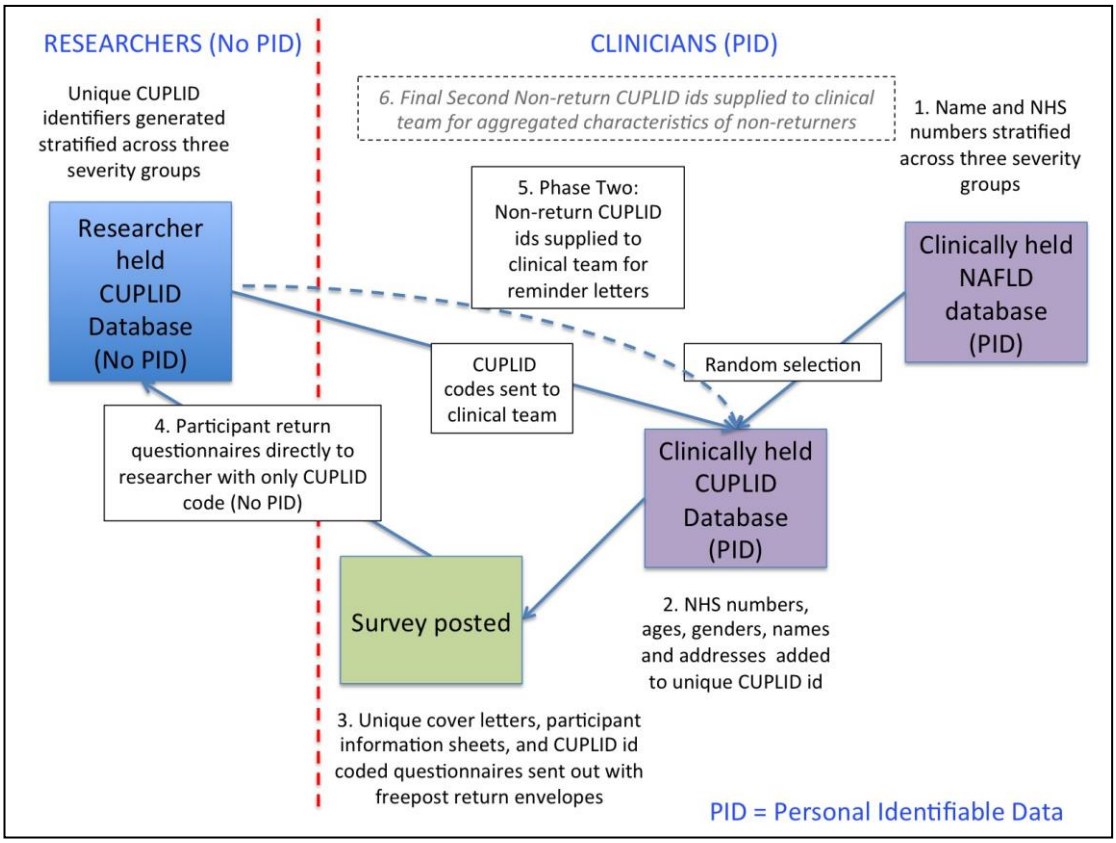


Figure 31: Procedural process for the CUPLID survey

5.3.5 Full survey

5.3.5.1 Setting for survey sample

Three NHS sites conducted the full CUPLID survey using the methodology conducted in the pilot phase; University Hospital Southampton, Queen Alexandra Hospital Portsmouth, and Royal Infirmary of Edinburgh. Three sites were chosen to allow greater generalisability and the specific locations based on established collaborations between the site clinical hepatology teams and our research group. Each site had established NAFLD databases of patients who had attended an outpatient appointment at the site and had been given a clinical diagnosis of NAFLD. The full CUPLID mixed methods study protocol and the CUPLID survey procedural document were supplied to the Principal Investigator (PI) at each site and RP was available to answer any questions that arose. Additionally RP worked closely with the PI at both University Hospital Southampton and

Queen Alexandra Hospital to create the CUPLID database and send out the survey, being present in both sites during this time. There was minimal inter-site difference in the conduct of the survey except that envelopes were printed rather than handwritten in Portsmouth. Since this did not affect the resulting return rate the reminder letters in Southampton were also printed. Secondly in Edinburgh, the reminder packs did not contain a second copy of the questionnaire in order to reduce the resource implications, and the reminder letters were altered to reflect this with prior ethical approval.

5.3.5.2 Eligibility criteria

Eligibility criteria are shown in Table 19.

Table 19: Eligibility criteria for participation in the quantitative phase of CUPLID

Inclusion criteria
Males & Females Adults ≥ 18 years Any ethnicity Any socio-economic status Any coffee drinking status (coffee drinkers and non-drinkers) Diagnosis of Non-Alcoholic Fatty Liver Disease (NAFLD) by the existing clinic care team 1. Evidence of hepatic steatosis (imaging/histology) 2. No causes for secondary hepatic fat accumulation (viral hepatitis, medications, genetics) 3. Exclusion of significant alcohol consumption (<20g/day (2.5 units) women, <30 g/day (3.75 units) men) 4. Patient has had a liver Fibroscan
Exclusion criteria
Outside stated age range Not having been given a diagnosis of Non-Alcoholic Fatty Liver Disease (NAFLD) Not having had a liver Fibroscan

5.3.6 Sample size calculation

Two a priori hypotheses were generated and the first of these was used to determine the sample size for the survey. These were that the proportions of participants agreeing to a) the achievability for drinking two additional cups of caffeinated coffee if they were advised that it was beneficial to their health, and b) interest in being involved in a future randomised controlled trial in which coffee was tested as a treatment, would be different between current coffee drinkers and non-coffee drinkers.

A sample size calculation was performed for the number of survey participants required using Cochran's formula (1977)[281]. The calculation took into account a margin of error of 5% and an alpha value of 0.05 (5%), the latter being the acceptable risk that the true margin of error exceeds the acceptable margin of error. Variance in response, was unknown prior to the conduct of the pilot survey, and was assumed at its maximal value of 0.5 (maximum variation will occur when half the respondents answer 'yes' and half respondents answer 'no').

The Cochran equation for survey sample size:

$$n = \frac{(\text{t-value for alpha level})^2 * (\text{proportion 1} * \text{proportion 2})}{(\text{margin of error})^2}$$

$$n = \frac{(1.96)^2 * (0.5 * 0.5)}{(0.05)^2}$$

$$n = \frac{3.84 \times 0.25}{0.0025}$$

$$n = 384$$

No adjustment for population size was needed due to the calculated number of surveys being less than 5% of the total estimated population at risk[281], calculated as 5% of the adult population of UK, equating to approximately 2,600,000 people. This stems from research suggesting 25% of the total adult population has any form of NAFLD including benign steatosis, and 20% will progress to fibrosis (0.25 x 0.20 = 0.05) and a total UK adult population of 52,000,000.

Based on the proposed sample size of 384, there was a > 85% power to correctly reject the null hypothesis (no difference between coffee drinkers and non-coffee drinkers) when the difference between proportions was at least 20%. This was based on the assumption that in the total sample there would be a 1:4 ratio of non-coffee drinkers to coffee drinkers.

5.3.6.1 Data analysis

The survey provided a range of quantitative variables as shown in Table 20. The survey was analysed by producing a number of summary statistics for coffee consumption variables including the frequency of coffee consumption, volume, and preparation types, and specifically proportions of participants in each of the groups 0 cups a day, 1-3 cups a day, and ≥4 cups a day (based on the coffee intake the day prior to completing the questionnaire). Summary statistics were also generated for frequency of response for questions about increasing coffee intake, reasons why this might not be achievable, and aspects of acceptability, design and assistance within a future randomised controlled trial. The survey also allowed a summary of coffee consumption across a range of socio-demographic and behavioural variables, and across NAFLD severity. NAFLD severity was not self-reported but intrinsic in the design of the survey in which patients on NAFLD databases were stratified into three liver stiffness groups before being randomly selected, as described previously. Co-morbidities of heart disease, stroke and type II diabetes were self-reported. BMI was calculated from self-reported height and weight and weight status was calculated following the standard cut-offs of healthy weight 18.5-24.9, overweight 25-29.9, and obesity ≥30 Kg/m^2. The AUDIT-C score was dichotomised between <5 and ≥5, with the latter recognised as indicating higher risk alcohol consumption.

Table 20: Dependent and Independent variables for the quantitative data analysis

		Independent Variable												
Dependent Variable	**Type of variable**	**Gender**	**Age groups**	**Ethnicity**	**Work**	**Housing**	**People at home**	**Smoking**	**Alcohol**	**Weight status***	**Diabetes**	**CHD**	**Stroke**	**Disease severity ****
Regular coffee drinker?	**Binary**	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
0, 1-3 and ≥4 cups a day	**Ordinal**	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Coffee/tea/cola/energy drinks	**Continuous**	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Views coffee on health	**Ordinal**	✔	✔	X	X	X	X	X	X	X	X	X	X	✔
Views coffee on liver health	**Ordinal**	✔	✔	X	X	X	X	X	X	X	X	X	X	✔
Liver effect on coffee drinking	**Ordinal**	✔	✔	X	X	X	X	X	X	X	X	X	X	✔
Achievability of +2 coffee cups	**Binary**	✔	✔	X*	X*	X*	X*	X*	X*	X*	X*	X*	X*	✔
Barriers to not + 2 coffee cups	**Nominal**	✔	✔	X	X	X	X	X	X	X	X	X	X	✔
Acceptability intervention	**Binary**	✔	✔	X	X	X	X	X	X	X	X	X	X	✔
Acceptability randomisation	**Binary**	✔	✔	X	X	X	X	X	X	X	X	X	X	✔
Form of extra 2 cups in study	**Nominal**	✔	✔	X	X	X	X	X	X	X	X	X	X	✔
Assistance needed in study	**Nominal**	✔	✔	X	X	X	X	X	X	X	X	X	X	✔
Interest in being part of this type of study	**Binary**	✔	✔	X*	X*	X*	X*	X*	X*	X*	X*	X*	X*	✔

**From BMI calculated from self-reported height and weight;*

***Clinical diagnosis used to stratify survey invitation; all other factors self-reported*

✔ = data described/analysed X = data not described/analysed X* = data available in appendix following post hoc analysis

Survey data on the number of cups, cup size, and coffee preparation type, consumed the day prior to completing of the questionnaire, was also converted to a coffee units a day measure to allow better comparison of coffee drinking patterns across the sample, and specifically this was divided into participants consuming 0 units a day, >0 to <4 units, and ≥4 units a day. The coffee unit measure was developed in parallel to the CUPLID study and is described in chapter three and data used to calculate each preparation type is available in appendix M. Misclassification of coffee intake comparing reported cups a day with coffee unit standardised cups a day with CUPLID participants was also identified using similar methodology to chapter 3.

Microsoft Excel[282] was used to manage the data and the statistical package SPSS version 24[260] was used to produce the summary statistics and conduct the analysis.

5.4 Results

Nb: Only the most relevant results have been presented or described in this section. Additional data can be found in the appendices as indicated in the text.

A total of 688 questionnaires (including the 51 in the pilot survey) were sent to potential participants across the three NHS sites (based on a conservative expected return rate of 55%) and 393 questionnaires were returned (actual return rate = 57%). Table 21 shows the number of questionnaires sent out and returned from each NHS site and the corresponding return rates, including by liver stiffness group. Return rates were similar across sites with the greatest return rate from Portsmouth Queen Alexandra Hospital. Overall return rates dropped with increasing severity.

Table 21: Number of questionnaires sent and returned across three NHS sites

	Number of questionnaires sent (% sent across all sites)	Number of questionnaires returned (% returned across all sites)	Liver stiffness <7 kPa return rate %	Liver stiffness 7-13 kPa return rate %	Liver stiffness >13 kPa return rate %	Total return rate %
University Hospital Southampton	267 (39)	147 (37)	53	56	57	55
Queen Alexandra Hospital Portsmouth	263 (38)	166 (42)	70	65	53	63
Royal Infirmary of Edinburgh	158 (23)	80 (20)	67	42	44	51
All sites	688 (100)	393 (100)	63	54	51	57

5.4.1 Differences between participants and non-participants

Aggregated age, gender and liver stiffness severity data were available to compare participants and non-participants to help identify any differences between the two groups, and therefore generalisability of the results, and are shown in Table 22. Participants were slightly older compared with non-participants, whilst the distribution of gender was similar. The three severity groups were well represented by both participants and non-participants with a slight shift towards lower severity in participants.

Table 22: Number and proportion of participants and non-participants by gender, age and liver stiffness

	Number male (%)	Number Female (%)	Mean age (years)	Number liver stiffness <7 KPa (%)	Number liver stiffness 7-13 KPa (%)	Number liver stiffness >13 KPa (%)
Participants	221 (56)	168 (44)	60	151 (38)	136 (35)	105 (27)
Non-participants	180 (61)	115 (39)	52	92 (31)	107 (36)	96 (3)

5.4.2 Characteristics of participants

5.4.2.1 Socio-demographic characteristics of participants

Summary socio-demographic characteristics of patients with NAFLD participating in the CUPLID survey are shown in Table 23. The sample consisted of 393 participants, including 305 (78%) coffee drinkers and 88 (22%) non-coffee drinkers. Amongst coffee drinkers, 255 (84%) consumed mainly caffeinated and 47 (16%) decaffeinated types. There were more male participants at 221 (56%) compared to females at 168 (43%) and more males drinking coffee at 185 (84%) compared to females at 117 (70%).

Figure 32 presents coffee drinking status by age. There was a trend for an increase in number of participants with age and most were aged 45-74 reflecting the secondary care NAFLD population. After the age of 35 years, there was a trend of coffee drinking prevalence to reduce across the age groups, and decaffeinated coffee consumption to increase amongst those drinking coffee.

Table 23: Socio-demographic characteristics by coffee drinking status

Characteristic		Total sample		Non-coffee drinker		Any coffee-drinker		Caffeinated coffee-drinker		Decaffeinated coffee-drinker	
		N	%	N	%	N	%	N	%	N	%
Total sample		393	100	88	22.4	305	77.6	255	84.4	47	15.5
Gender N=390	Male	221	56.4	36	16.3	185	83.7	155	84.2	29	15.8
	Female	168	43.3	51	30.4	117	69.6	98	84.5	18	15.5
	Other	1	0.3	0	0.0	1	100	1	100	0	0
Age group N=390	25-34	11	2.8	0	0	11	100	10	90.9	1	9.1
	35-44	21	5.4	6	28.6	15	71.4	13	86.7	2	13.3
	45-54	72	18.5	9	12.5	63	87.5	54	87.1	8	12.9
	55-64	142	36.4	33	23.2	109	76.8	97	89.0	12	11.0
	65-74	107	27.4	26	24.3	81	75.7	63	78.8	17	21.3
	75-84	36	9.2	12	33.3	24	66.7	16	69.6	7	30.4
	85+	1	0.3	1	100	0	0	0	0	0	0
Ethnicity N=384	White	363	94.5	79	21.8	284	78.2	241	85.5	41	14.5
	Non-white	21	5.5	5	23.8	16	76.2	12	80.0	3	20.0
Employment status N=384	Working	179	45.5	33	18.4	146	81.6	127	87.0	19	13.0
	Retired	151	38.4	40	26.5	111	73.5	89	80.9	21	19.1
	Other	54	14.1	12.0	22.2	42.0	77.8	36.0	87.8	5.0	12.2
Home ownership N=382	Own	265	69.4	57	21.5	208	78.5	173	83.6	34	16.4
	Rent public	66	17.3	12	19.7	49	80.3	46	93.9	3	6.1
	Rent private	24	6.3	17	45.9	20	54.1	17	85.0	3	15.0
	Other	25	6.5	5.0	19.2	21.0	80.8	14.0	77.8	4.0	22.2
Persons in household N=380	Mean (SD)	2.3	(1.1)	2.1	(1.0)	2.4	(1.1)	2.4	(1.1)	2.4	(1.1)

There were 384 participants who provided ethnicity data and of these 363 (95%) described themselves as white and 21 (6%) non-white. There were 179 (46%) participants in paid work, either employed or self-employed, and 151 retired (38%). Coffee drinking prevalence in those who were retired was lower than those working, but this may be linked to age. There were 265 (70%) participants who owned their own homes either outright or with a mortgage.

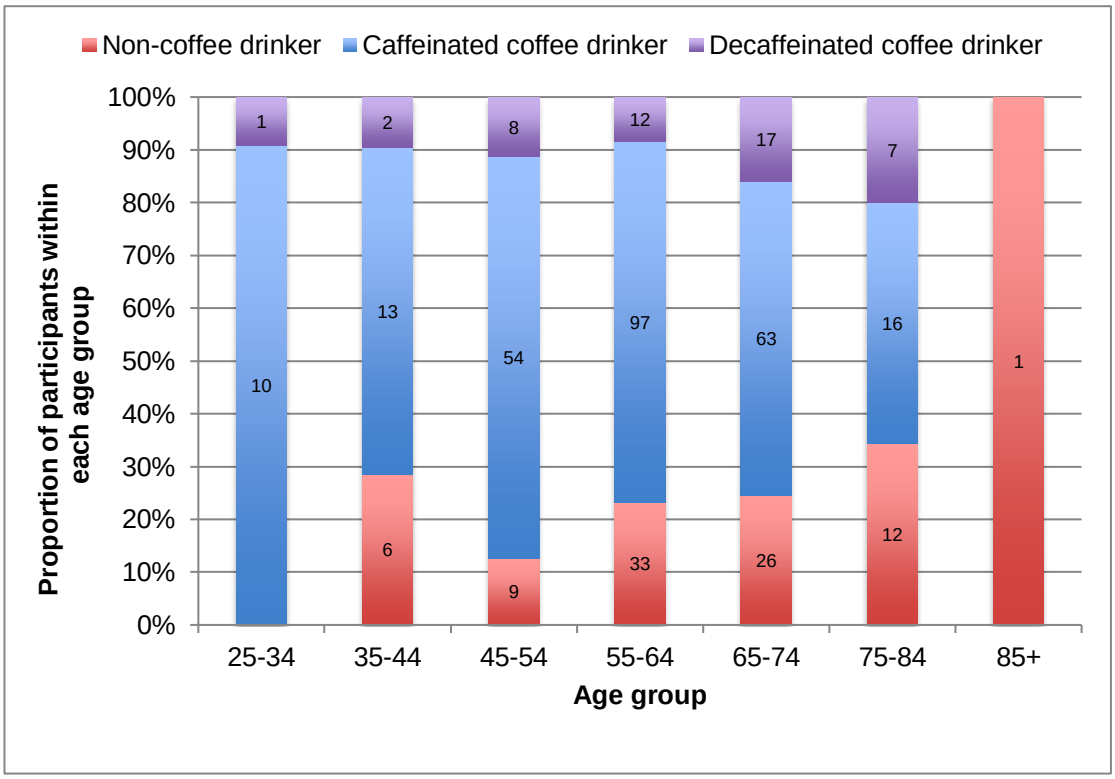


Figure 32: Distribution of coffee drinking status by age

*Data labels represent number of participants

5.4.2.2 Clinical and behavioural characteristics

Table 24 shows clinical and health characteristics of the sample. The sample was represented by each of the three liver stiffness severity groups with 151 (39%) from liver stiffness group 1 (<7 kPa), 136 (35%) from liver stiffness group 2 (7-13 kPa) and 105 (27%) from liver stiffness group 3 (>13 kPa). The proportion of coffee drinkers decreased

as NAFLD severity increased (Figure 33). A fifth of coffee drinkers in the most severe group were drinking mainly decaffeinated coffee, higher than the other liver stiffness groups.

There were 113 (31%) participants who were overweight, and 226 (61%) who were obese. In total 53% of participants had at least one co-morbid condition, with 168 (44%) of all participants having self-reported type II diabetes. There were lower proportions of coffee drinkers in those with obesity compared to non-obesity, and with type II diabetes compared to no diabetes. Heart disease was a co-morbid condition in 68 (18%) participants, and stroke in 15 (4%). Coffee drinking prevalence did not appear to differ comparing those with or without heart disease but a lower proportion of participants with a diagnosis of stroke drank coffee compared to those without stroke, but were still more likely to be coffee drinkers than not.

Smoking prevalence was 8% in the sample (29 participants) and there was no clear difference in coffee drinking prevalence between those who smoked and those who did not. The sample also consisted of 108 (27%) of participants with an Audit-C score of 5 or more consistent with higher risk alcohol intake. Those in this higher risk alcohol category had a higher prevalence of coffee drinking, and caffeinated coffee drinking.

Figure 33: Proportion of coffee drinkers and non-coffee drinkers within each liver stiffness group

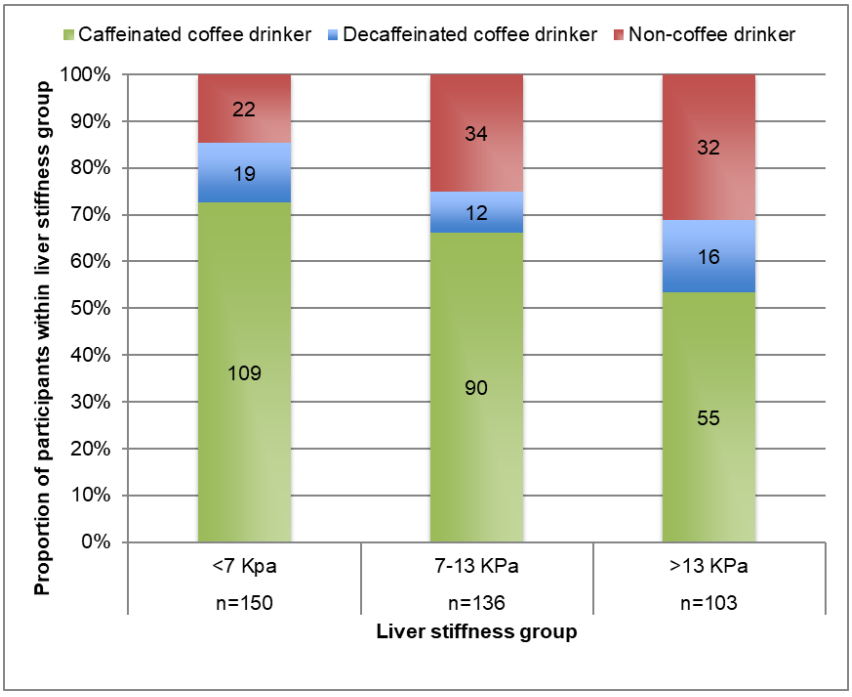


Table 24: Clinical and behavioural characteristics by coffee drinking status

Characteristic		Total sample		Non-coffee drinker		Any coffee-drinker		Caffeinated coffee-		Decaffeinated	
		N	%	N	%	N	%	N	%	N	%
Total sample		393	100	88	22.4	305	77.6	255	84.4	47	15.5
Liver Stiffness* N=392	<7 KPa	151	38.5	22	14.6	129	85.4	109	85.2	19	14.8
	7-13 KPa	136	34.7	34	25.0	102	75.0	90	88.2	12	11.8
	>13 KPa	105	26.8	32	30.5	73	69.5	55	77.5	16	22.5
Weight status** N=369	Underweight	3	0.8	0	0	3	100	2	66.7	1	33.3
	Healthy weight	27	7.3	5	18.5	22	81.5	17	81.0	4	19.0
	Overweight	113	30.6	20	17.7	93	82.3	83	90.2	9	9.8
	Obese	226	61.2	54	23.9	172	76.1	141	82.5	30	17.5
Diabetic*** N=381	Yes	168	44.1	31	18.5	137	81.5	115	84.6	21	15.4
	No	213	55.9	52	24.4	161	75.6	136	85.5	23	14.5
Coronary Heart Disease*** N=383	Yes	68	17.8	14	20.6	54	79.4	43	81.1	10	18.9
	No	315	82.2	69	21.9	246	78.1	209	85.7	35	14.3
Stroke*** N=383	Yes	15	3.9	5	33.3	10	66.7	8	88.9	1	11.1
	No	368	96.1	78	21.2	290	78.8	244	84.7	44	15.3
Smoking*** N=384	Yes	29	7.6	6	20.7	23	79.3	22	95.7	1	4.3
	No	355	92.4	78	22.0	277	78.0	230	83.9	44	16.1
Alcohol *** N=389	Audit C score ≥5	108	27.2	17	15.7	91	84.3	79	87.8	11	12.2
	Audit C score <5	281	72.2	70	24.9	211	75.1	173	82.8	36	17.2

** Clinical diagnosis used in sampling stratification*
*** From BMI calculated from self-reported height and weight*
**** Self-reported*

5.4.3 Quantification of coffee intake

Coffee was regularly consumed by 305 (78%) of participants. Most participants who consumed coffee did so everyday (median days in week 7 (IQR 4-7)) and 1 or 2 cups a day (median cups a day 2.0 (IQR 1.0 to 3.0)) as presented in Figure 34. Cups a day did not differ between caffeinated and decaffeinated coffee drinkers with the exception of decaffeinated coffee drinkers on weekend (non-working) days where intake was slightly lower than caffeinated coffee drinkers. Most participants had a similar weekday and weekend consumption (median difference in weekday minus weekend cups = 0 cups a day (IQR 0 to 1)). In liver stiffness group 3, but not the less severe groups, higher level of alcohol intake (AUDIT-C score ≥5) was associated with a higher median coffee intake (2.5 cups a day), and lower alcohol intake (AUDIT`-C score <5) was associated with lower median coffee intake (1 cup a day).

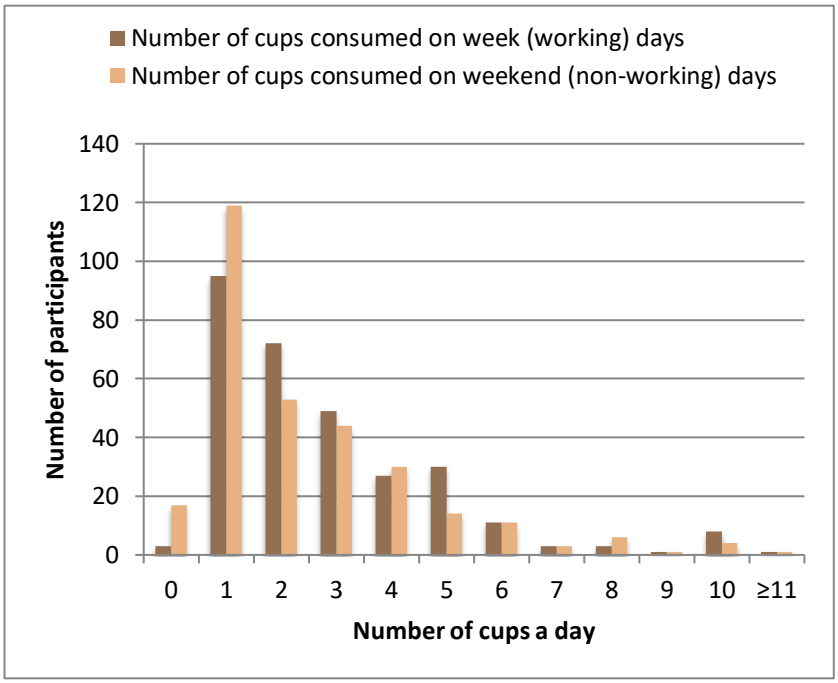


Figure 34: Number of cups a day consumed on week and weekend days

5.4.3.1 Coffee consumption the day before questionnaire

There were 273 coffee drinkers (90%) who had consumed coffee the day before completing the questionnaire. Amongst those who did consume day before coffee, 215 (79%) consumed only one preparation type, and median consumption was 2.0 cups (IQR 1.0 to 3.0)). Number of cups consumed the day before completing the questionnaire is shown in Figure 35.

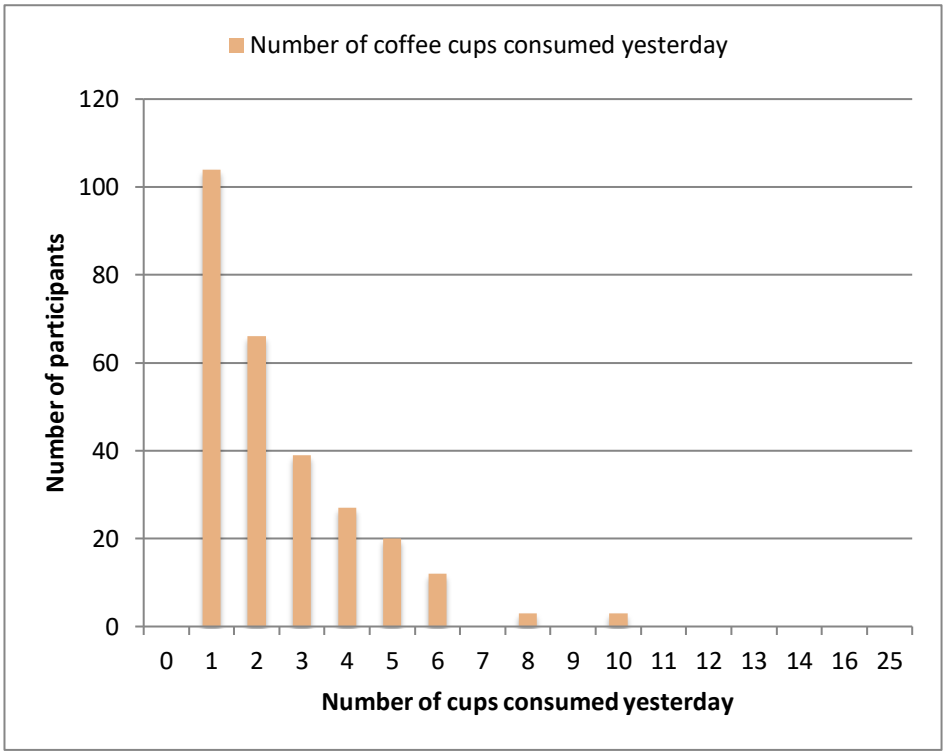


Figure 35: The number of coffee cups consumed the day before completing the questionnaire

Table 25 and Table 26 present coffee intake by cups a day across socio-demographic, and clinical and behavioural characteristics, respectively. Including regular coffee consumers

who did not consume any coffee the day before completing the questionnaire as well as those who did, 240 (61%) participants consumed 1-3 cups, and 65 (17%) consumed ≥4 cups, whilst 88 (22%) were non-coffee drinkers. Across liver severity groups, the proportions drinking 1-3 cups or ≥4 cups the day before the questionnaire were similar.

Table 25: Socio-economic characteristics of participants by cups of coffee consumed yesterday

Characteristic		0 cups/units a day		1-3 cups a day		% Instant	≥4 cups a day		% Instant
		N	%	N	%		N	%	
Total sample		88	22.4	240	61.1	51	65	16.5	69.5
Gender N=390	Male	36	16.3	145	65.6	51.9	40	18.1	67.4
	Female	51	30.4	92	54.8	49	25	14.9	72.9
	Other	0	0	1	100	-	0	0	-
Age N=390	25-34	0	0	9	81.8	33.3	2	18.2	100
	35-44	6	28.6	12	57.1	34.7	3	14.3	75
	45-54	9	12.5	51	70.8	51.6	12	16.7	55.4
	55-64	33	23.2	77	54.2	51.8	32	22.5	73.1
	65-74	26	24.3	69	64.5	54.1	12	11.2	74.2
	75-84	12	33.3	21	58.3	53.3	3	8.3	33.3
	85+	1	100	0	0	-	0	0	-
Ethnicity N=384	White	79	21.8	220	60.6	51	64	17.6	69
	Non-white	5	23.8	16	76.2	45.8	0	0	-
Employment status N=384	Working	33	18.4	118	65.9	46.9	28	15.6	65
	Retired	40	26.5	93	61.6	53.3	18	11.9	66.7
	Other	12	22.2	26	48.1	55.6	16	29.6	63.6
Home ownership N=382	Own	57	21.5	168	63.4	50.3	40	15.1	70
	Rent public	12	19.7	35	57.4	57.3	14	23	60.2
	Rent private	17	45.9	15	40.5	41.1	5	13.5	80
	Other	5	19.2	18	69.2	72.2	3	11.5	87.5
Persons in household	Mean (SD)	2.1	-1	2.4	-1.2	-	2.3	-1	-

Table 26: Clinical and behavioural characteristics by cups of coffee consumed yesterday

Characteristic		0 cups/units a day		0-3 cups a day		% Instant	≥4 cups a day		% Instant
		N	%	N	%		N	%	
Total sample		88	22.4	240	61.1	51.0	65	16.5	69.5
Liver Stiffness N=392	<7 KPa	22	14.6	98	64.9	52.2	31	20.5	72.7
	7-13 KPa	34	25.0	86	63.2	49.6	16	11.8	67.7
	>13 KPa	32	30.5	55	52.4	52.1	18	17.1	65.6
Weight status N=369	Underweight	0	0.0	3	100.0	66.7	0	0.0	-
	Healthy weight	5	18.5	19	70.4	33.3	3	11.1	93.3
	Overweight	20	17.7	74	65.5	41.1	19	16.8	71.3
	Obese	54	23.9	134	59.3	59.3	38	16.8	65.4
Diabetic N=381	Yes	31	18.5	105	62.5	50.5	32	19.0	69
	No	52	24.4	131	61.5	50.9	30	14.1	70.3
Coronary Heart Disease N=383	Yes	14	20.6	45	66.2	47.3	9	13.2	94.4
	No	69	21.9	193	61.3	51.5	53	16.8	65.4
Stroke N=383	Yes	5	33.3	8	53.3	83.3	2	13.3	91.7
	No	78	21.2	230	62.5	49.8	60	16.3	68.9
Smoking N=384	Yes	6	20.7	15	51.7	53.8	8	27.6	68.8
	No	78	30.6	123	48.2	50.5	54	21.2	69.8
Alcohol N=389	Audit C score ≥5	17	15.7	69	63.9	50.3	22	20.4	56.6
	Audit C score <5	70	24.9	170	60.5	50.9	41	14.6	77.4

The different coffee preparation types consumed the day before completing the questionnaire are presented in Table 27 and displayed in Figure 36. The most frequently consumed coffee type was instant coffee, which was consumed by 169 (62%) of those participants who had consumed coffee the day before and comprised 61% of all coffee cups consumed. Lattes were the next most frequently consumed by 42 (15%) of participants and 9% of all coffee cups consumed.

Table 27: Coffee preparation types consumed the day before questionnaire for all coffee types

Any coffee preparation	Participants consuming type yesterday		Cups consumed yesterday		Median number of cups consumed yesterday	Range of cups consumed yesterday	
	N	%	N	%		Lower	Upper
Any coffee type	273	100	683	100	2.0 (1.0 to 3.0)	1	10
Instant	169	61.9	416	60.9	2.0 (1.0 to 3.0)	1	10
Latte	42	15.4	62	9.1	1.0 (1.0 to 1.3)	1	3
Filter	29	10.6	49	7.2	1.0 (1.0 to 2.0)	1	4
Capsule/pod	29	10.6	53	7.8	1.0 (1.0 to 2.0)	1	5
Cappuccino	19	7.0	30	4.4	1.0 (1.0 to 2.0)	1	6
Americano	16	5.9	20	2.9	1.0 (1.0 to 1.0)	1	3
Flat White	12	4.4	17	2.5	1.0 (1.0 to 1.5)	1	3
Cafetière	10	3.7	17	2.5	1.5 (1.0 to 2.0)	1	2
Mocha	6	2.2	9	1.3	1.0 (1.0 to 2.3)	1	3
Single espresso	5	1.8	8	1.2	1.0 (1.0 to 2.5)	1	4
Double espresso	2	0.7	2	0.3	1.0 (1.0 to 1.0)	1	1

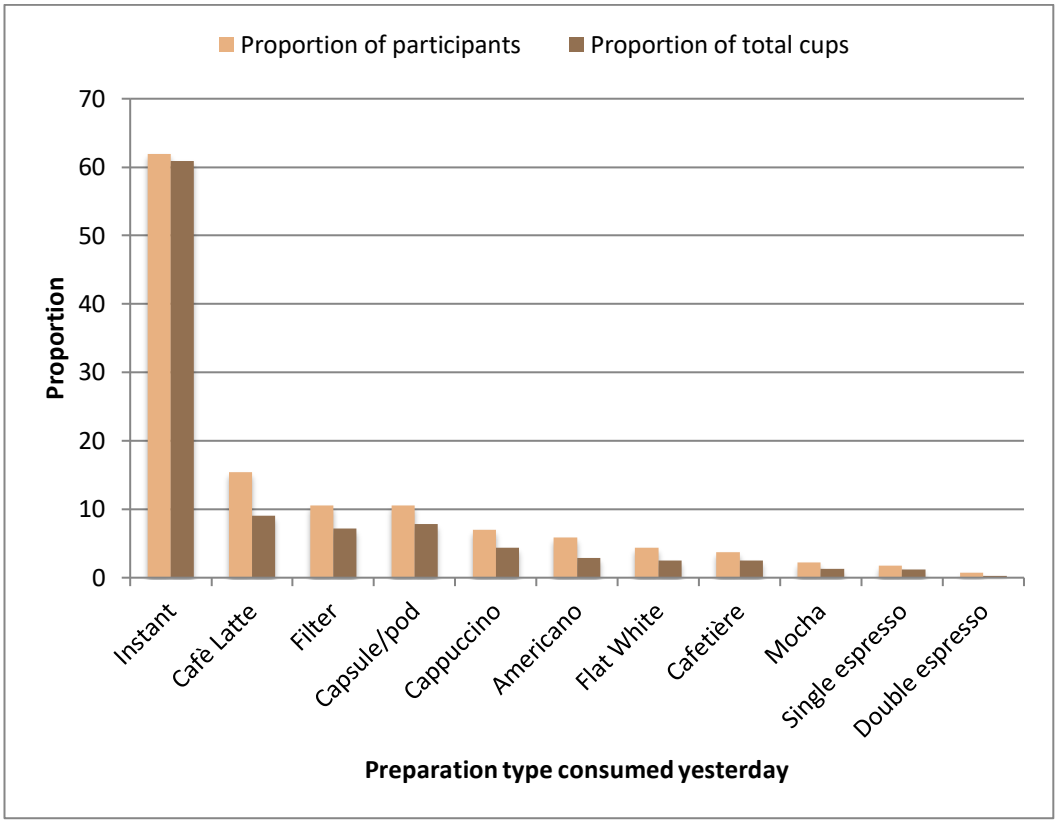


Figure 36: Proportion of participants and cups consuming each coffee type the day before completing the questionnaire

5.4.3.2 Regular coffee consumption

Participants consumed a range of 1 to 6 coffee preparation types on a regular basis, with over half of coffee drinkers consuming only one type. More caffeinated than decaffeinated coffee drinkers consumed more than one type of coffee preparation, and the range of decaffeinated coffee types was lower.

The distribution of different coffee preparation types is presented in Table 28. Instant coffee was consumed on a regular basis by 202 (66%) of participants. Latte was the next most regularly consumed coffee type by 74 (24%), cappuccino by 46 (15%), coffee-pod/capsule coffee by 37 (12%), Americano by 33 (11%) and filter coffee by 31 (10%) of participants. The remaining types were consumed by a much smaller proportion of participants. Figure 37 displays the proportion of participants drinking each preparation type on a regular basis, and the proportion drinking only one type.

Table 28: Coffee preparation types consumed regularly

	Participants consuming type regularly (any coffee)		Participants consuming type regularly (caffeinated coffee)		Participants consuming type regularly (decaffeinated coffee)	
	N (n=305)	% of all coffee drinkers	N (n=255)	% of all caffeinated coffee drinkers	N (n=47)	% of all decaffeinated coffee drinkers
Instant	202	66.2	167	65.5	33	70.2
Latte	74	24.3	65	25.5	8	17.0
Filter	31	10.2	25	9.8	6	12.8
Capsule/pod	37	12.1	33	12.9	4	8.5
Cappuccino	46	15.1	41	16.1	4	8.5
Americano	33	10.8	29	11.4	4	8.5
Flat White	29	9.5	26	10.2	3	6.4
Cafetière	23	7.5	21	8.2	2	4.3
Mocha	12	3.9	11	4.3	1	2.1
Single espresso	6	2.0	6	2.4	0	0.0
Double espresso	10	3.3	10	3.9	0	0.0
Iced coffee	1	0.3	1	0.4	0	0.0

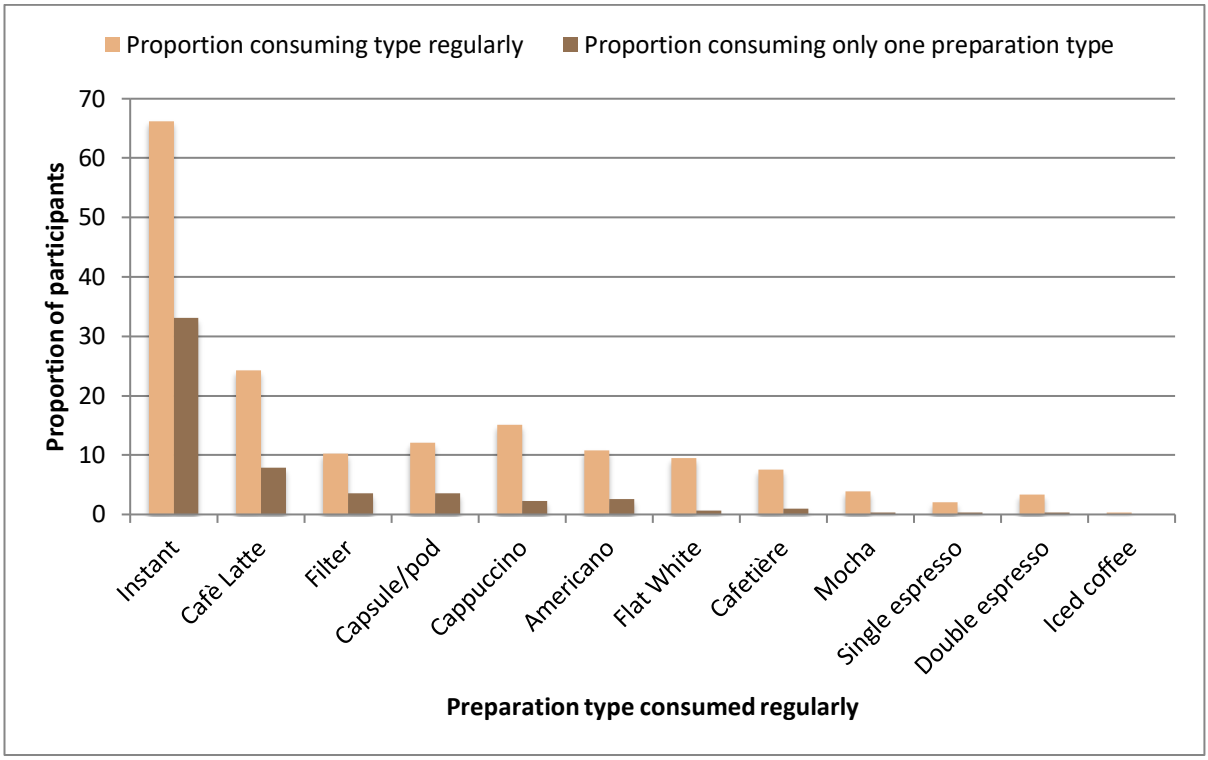


Figure 37: Proportion of participants drinking any preparation type regularly and proportion drinking only one preparation type

5.4.3.3 Additional ingredients and drinking location

Ingredients added to coffee, such as milk and sugar, and regular locations of consumption, are presented in Table 29. Most coffee drinkers had some form of milk added to coffee with only 45 (15%) drinking their coffee black. Semi-skimmed was the most common choice of milk, followed by skimmed, and full fat. Use of cream, soya, or Coffee Mate was uncommon amongst participants.

Most participants consumed their coffee unsweetened. Among participants adding some form of sweetness, sugar or sweetener were chosen by 69 (23%) and 64 (21%) of participants respectively.

Home was the most frequent consumption location with 268 (88%) of coffee drinkers consuming coffee on a regular basis. Coffee shops, work and restaurants were locations where 136 (45%), 114 (37%) and 54 (18%) of participants consumed coffee on a regular basis.

Table 29: Additional ingredients regularly added to coffee and location of consumption

Any coffee		Participants drinking any coffee		Participants drinking caffeinated coffee		Participants drinking decaffeinated coffee	
		N	%	N	%	N	%
Milk added	None	45	14.9	38	14.8	7	15.2
	Semi	164	54.3	142	55.5	22	47.8
	Skim	51	16.9	42	16.4	9	19.6
	Full fat	30	9.9	24	9.4	6	13.0
	Cream	2	0.7	2	0.8	0	0.0
	Soya	1	0.3	0	0.0	1	2.2
	Coffee mate	3	1.0	3	1.2	0	0.0
	Not sure	6	2.0	5	2.0	1	2.2
Sugar added	None	166	55.0	137	53.5	29	63.0
	Sweetener	64	21.2	53	20.7	11	23.9
	Sugar	69	22.8	63	24.6	6	13.0
	Syrup	1	0.3	1	0.4	0	0.0
	Honey	2	0.7	2	0.8	0	0.0
Locations consumed	Home	268	87.9	226	88.6	42	89.4
	Coffee shop	136	44.6	116	45.5	20	42.6
	Work	114	37.4	97	38.0	17	36.2
	Restaurant	54	17.7	45	17.6	9	19.1

5.4.4 Misclassification of coffee intake

Comparing caffeinated coffee cups consumed the day before the participant completed the questionnaire with coffee cups standardised by the coffee unit measure, 48% of participants had no misclassification, and 52% were misclassified, mostly with intakes underestimated by one cup or two cups (Table 30). Misclassification was similar across subgroups, with slightly more misclassification in males compared to females, participants with AUDIT-C score ≥5, and participants consuming a higher number of daily cups (appendix V).

Table 30: Proportion of participants misclassified across reported caffeinated cups compared with coffee unit-standardised cups a day

Volume and preparation type (coffee unit) standardised cups a day in CUPLID	Reported cups a day in CUPLID											
	0	1	2	3	4	5	6	7	8	9	10	Tot
0	-	0.43										0.43
1	-	22.9										22.9
2	-	9.52	9.52									19.0
3	-	3.46	9.96	5.63	0.43							19.4
4	-		3.03	5.19	3.90	0.43						12.5
5	-		0.87	2.16	0.87	3.03						6.93
6	-			1.30	2.60	0.87	3.03					7.79
7	-		0.43	0.43	0.87	1.30						3.03
8	-						0.87					0.87
9	-				0.43							0.43
10	-			0.43		1.73						2.16
≥11	-				0.43	0.43	1.30		0.87		1.30	4.33
≥2 cups over	-											0.00
1 cup over	-	0.43			0.43	0.43						1.30
No	-	22.9	9.52	5.63	3.90	3.03	3.03					48.0
1 cup under	-	9.52	9.96	5.19	0.87	0.87						26.4
≥2 cups under	-	3.46	4.33	4.33	4.33	3.46	2.16		0.87		1.30	24.2
Total	-	36.3	23.8	15.1	9.52	7.79	5.19		0.87		1.30	100
% Misclassified*	-	36.9	60.0	62.8	59.0	61.1	41.6		100		100	
Base (N)	-	84	55	35	22	18	12	0	2	0	3	231

*Within corresponding reported cups a day column

No misclassification 1 cup misclassification ≥2 cups misclassification

5.4.5 Characteristics of tea, cola, and energy drink drinkers

5.4.5.1 Socio-demographic characteristics of tea, cola and energy drink drinkers

Socio-demographic characteristics of participants consuming tea, cola and energy drinks are presented in Table 31 along with participants drinking coffee for comparison. There were 312 (79%) participants who regularly consumed tea, 133 (34%) who consumed cola, and 24 (6%) who consumed energy drinks. More males consumed cola and energy drinks relative to females, and those drinking energy drinks were slightly younger compared to coffee and tea drinkers.

A lower proportion of cola and energy drink consumers were retired compared to tea and coffee drinkers. A lower proportion of energy drink consumers owned their own homes with most in private or public rental accommodation.

5.4.5.2 Clinical and behavioural characteristics of tea, cola and energy drink drinkers

Clinical and behavioural characteristics of tea, cola, and energy drink drinkers are presented in Table 32. The proportion of tea drinkers was similar across the three liver stiffness severity groups with minor differences across other beverages. There were few notable differences in other characteristics between consumers of different beverages.

Smoking prevalence was higher in the cola drinkers (11%) and energy drink consumers (13%) compared with coffee (8%) and tea drinkers (6%) but the numbers were quite small. Audit-C scores of ≥5 were also more prevalent in the energy drink group compared to tea and cola, but similar to coffee.

Table 31: Socio-demographic characteristics of tea, cola and energy drink consumers and in comparison to coffee drinkers

Characteristic		Total sample		Coffee drinker		Tea drinker		Cola drinker		Energy drink drinker	
		N	%	N	%	N	%	N	%	N	%
Total sample		393	100	305	77.6	312	79.3	133	33.8	24	6.1%
Gender N=390	Male	221	56.4	185	61.1	177	57.3	81	60.9	19	79.2
	Female	168	43.3	117	38.6	131	42.4	52	39.1	5	20.8
	Other	1	0.3	1	0.3	1	0.3	0	0	0	0
Age N=390	18-24	0	0	0	0.0	0	0	0	0	0	0
	25-34	11	2.8	11	3.6	6	1.9	7	5.3	3	12.5
	35-44	21	5.4	15	5.0	15	4.8	10	7.6	1	4.2
	45-54	72	18.5	63	20.8	58	18.7	33	25.0	11	45.8
	55-64	142	36.4	109	36.0	106	34.2	45	34.1	6	25.0
	65-74	107	27.4	81	26.7	91	29.4	31	23.5	2	8.3
	75-84	36	9.2	24	7.9	33	10.6	6	4.5	1	4.2
	85+	1	0.3	0	0.0	1	0.3	0	0	0	0
Ethnicity N=384	White	363	92.4	284	94.7	286	94.1	120	93.0	20	87.0
	Other	2	0.5	2	0.7	1	0.3	0	0	0	0
Employment status N=384	Working	179	45.5	146	48.8	142	46.7	71	54.2	15	65.2
	Retired	151	38.4	111	37.1	124	40.8	39	29.8	2	8.7
	Other	6	1.6	4	1.3	6	1.9	1	0.8	0	0
Home ownership N=382	Own	265	67.5	208	69.8	209	69.2	86	66.6	10	43.5
	Rent public	66	16.8	49	16.4	50	16.6	21	16.3	4	17.4
	Rent private	24	6.1	20	6.7	22	7.3	8	6.2	3	13.0
	Other	11	2.1	11	3.7	9	3.0	9	7.0	3	13.0
Persons in household	Mean (SD)	2.3	(1.1)	2.4	0.8	2.3	(1.1)	2.4	(1.1)	2.7	(1.5)

Table 32: Clinical and behavioural characteristics of tea, cola and energy drink consumers and in comparison to coffee drinkers

Characteristic		Total sample		Coffee drinker		Tea drinker		Cola drinker		Energy drink drinker	
		N	%	N	%	N	%	N	%	N	%
Total sample		393	100	305	77.6	312	79.3	133	33.8	24	6.1%
Liver Stiffness N=392	<7 KPa	151	38.5	129	85.4	117	77.5	46	39.3	6	13.0
	7-13 KPa	136	34.7	102	75.0	110	80.9	48	43.6	11	22.9
	>13 KPa	105	26.8	73	69.5	84	80.0	38	45.2	7	18.4
Weight status N=369	Underweight	3	0.8	3	1.0	2	0.7	0	0	0	0
	Healthy weight	27	7.3	22	7.6	22	7.6	11	8.9	2	8.7
	Overweight	113	30.6	93	32.1	93	32.1	34	27.4	7	30.4
	Obese	226	61.2	172	59.3	173	59.7	79	63.7	14	60.9
Diabetic N=381	Yes	168	44.1	137	46.0	134	44.5	58	45.3	9	39.1
	No	213	55.9	161	54.0	167	55.5	70	54.7	14	60.9
Coronary Heart Disease N=383	Yes	68	17.8	54	18.1	55	18.2	17	13.1	5	21.7
	No	315	82.2	246	82.6	248	81.8	113	86.9	18	78.3
Stroke N=383	Yes	15	3.9	10	3.4	12	4.0	4	3.1	1	4.3
	No	368	96.1	290	97.3	291	96.0	126	96.9	22	95.7
Smoking N=384	Yes	29	7.6	23	7.7	19	6.3	14	10.7	3	13.0
	No	355	92.4	277	93.0	285	93.8	117	89.3	20	87.0
Alcohol N=389	Audit C score ≥5	108	27.2	91	30.5	85	27.5	34	26.0	7	30.4
	Audit C score <5	281	72.2	211	70.8	224	72.5	97	74.0	16	69.6

5.4.6 Quantification of tea, cola and energy drinks

Number of participants drinking tea, cola and energy drinks and quantification of intake are shown in Table 33. Most tea drinkers consumed 3 cups a day most days and used the typical 227ml (8oz) home mug to consume it. Most tea drinkers consumed caffeinated black tea, or black and green tea, with decaffeinated black and/or green tea being much less common. Cola and energy drink tended to be consumed much less frequently both in terms of number of days in a week and times in a day and medium sized drinks (330ml) were the most commonly consumed. Three-quarters of all cola consumed was the sugar-free, 'diet', variety and the remaining quarter was sugared. Figure 38 presents the proportion of participants drinking different beverage types on a regular basis and those drinking only one type of beverage.

Table 33: Quantification of regular tea, cola and energy drink consumption

	Participants consuming beverage		Median days in week drinking (IQR)	Median cups/times a day weekday (IQR)	Median Cups/times a day weekend day (IQR)	Median size of cup/glass/bottle
	N	%				
Any tea	312	79.4	7.0 (7.0 to 7.0)	3.0 (2.0 to 5.0)	3.0 (2.0 to 5.0)	S+ (227mL home mug)
Caffeinated Black tea	241	61.3	7.0 (7.0 to 7.0)	3.0 (2.0 to 5.0)	3.0 (2.0 to 5.0)	S+ (227mL home mug)
Caffeinated green tea	8	2.0	7.0 (6.3 to 7.0)	3.0 (1.3 to 4.0)	2.0 (0.3 to 4.0)	S+ (227mL home mug)
Caffeinated Black & green tea	16	4.1	7.0 (7.0 to 7.0)	3.0 (2.0 to 4.0)	3.0 (2.0 to 4.75)	S+ (227mL home mug)
Decaffeinated Black tea	28	7.1	7.0 (7.0 to 7.0)	3.0 (2.0 to 4.0)	3.0 (2.0 to 4.0)	S+ (227mL home mug)
Decaffeinated green tea	2	0.5	7.0 (7.0 to 7.0)	2.0 (1.0)	2.0 (1.5 to 2.5)	S+ (227mL home mug)
Decaffeinated Black tea & green tea	4	1.0	7.0 (7.0 to 7.0)	4.0 (3.3 to 4.0)	4.0 (4.0 to 4.75)	S+ (227mL home mug)
Any cola	133	33.8	3.0 (2.0 to 5.0)	1.0 (1.0 to 2.0)	2.0 (1.0 to 3.0)	M (330mL)
Cola	34	8.7	2.0 (1.0 to 5.0)	1.0 (1.0 to 2.0)	2.0 (1.0 to 3.0)	M (330mL)
Diet cola	95	24.2	3.0 (2.0 to 5.0)	1.0 (1.0 to 2.0)	2.0 (1.0 to 3.0)	M (330mL)
Energy drinks	24	6.1	1.0 (1.0 to 3.8)	1.0 (1.0 to 1.0)	1.0 (0.3 to 2.0)	S-M (250-330ml)

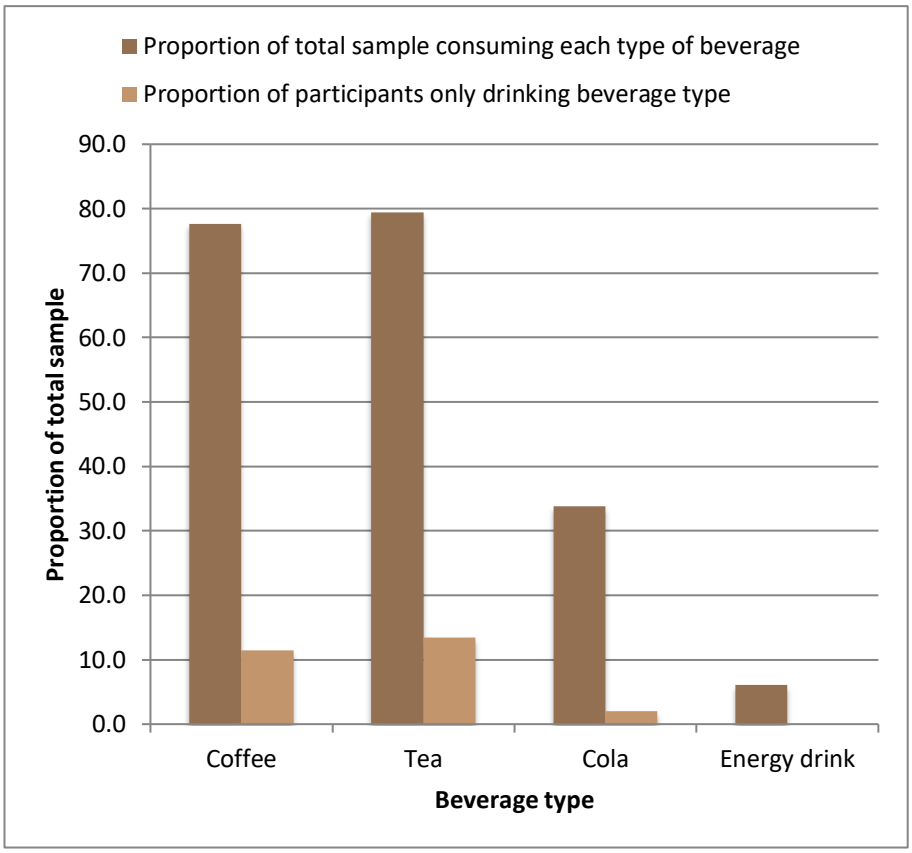


Figure 38: Proportion of participants drinking different beverage types

5.4.6.1 Additional ingredients and drinking location for tea

Data on additional ingredients added to tea, and drinking location, are presented in appendix P. Most tea drinkers had some form of milk added with only 36 (12%) drinking their tea black. Semi-skimmed was the most common choice of milk, followed by skimmed, and full fat was relatively uncommon. There were 199 (64%) participants who consumed their tea unsweetened and 54 (17%) and 57 (18%) using sugar and sweeteners respectively.

There were 303 (97%) of tea drinkers who consumed it at home with other locations of consumption much less frequently chosen by participants.

5.4.7 Range of caffeinated beverages consumed

Table 34 and Figure 39 presents the distribution of all coffee and all regular caffeinated beverage across participants. Approximately a quarter of participants consumed only one type of beverage. However, 66% of the sample (85% of all coffee drinkers) regularly consumed coffee and a second type of caffeinated beverage. Table 34 also shows the number of coffee drinking participants in each category and by coffee cups consumed the day before completing the questionnaire. A slightly higher proportion of coffee drinking participants who consumed ≥4 cups consumed no other beverages compared to those consuming 1-3 cups a day.

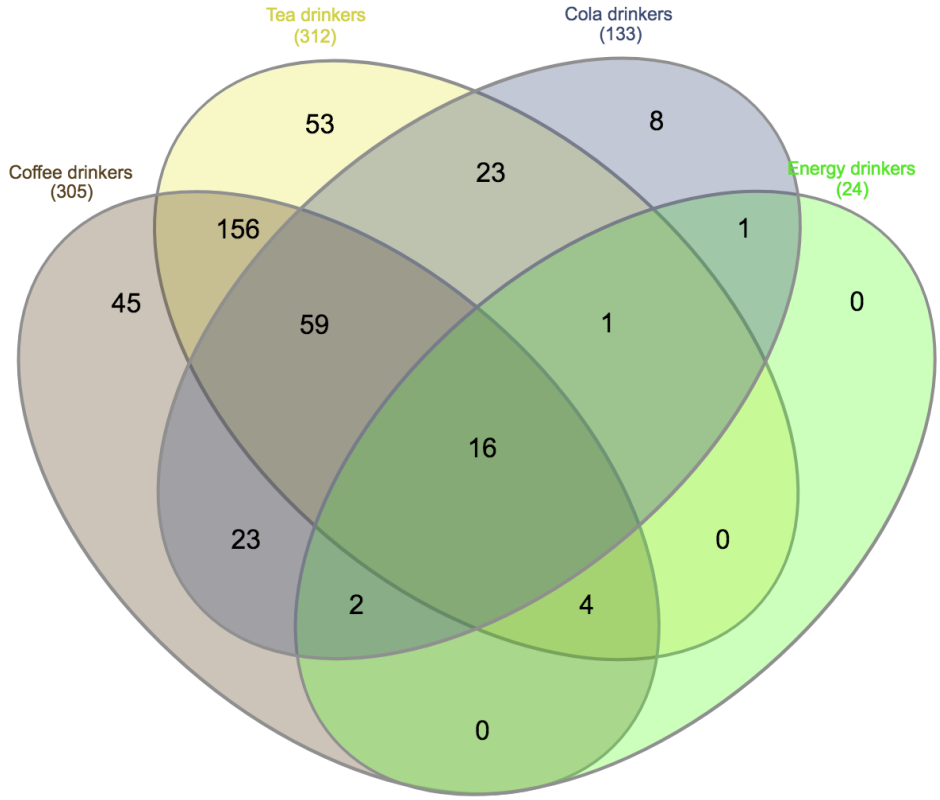


Figure 39: Venn diagram showing distribution of beverage consumption

Table 34: Range of caffeinated beverages consumed

Caffeinated beverage consumed	All Participants		0 coffee cups a day		1-3 coffee cups a day		≥4 coffee cups a day	
	N	% of all participants	N	% of all non-coffee drinkers	N	% of coffee drinkers yesterday	N	% of coffee drinkers yesterday
No caffeinated beverages	2	0.5	2	2.5	-	-	-	-
Coffee* only	45	11.5	-		30	12.5	15	25.9
Coffee* + tea	156	39.7	-		132	55.0	17	29.3
Coffee* + cola	23	5.9	-		8	3.3	15	25.9
Coffee* + energy drink	0	0.0	-		0	0.0	0	0.0
Coffee* + tea + cola	59	15.0	-		50	20.8	9	15.5
Coffee* + tea + energy drink	4	1.0	-		3	1.3	1	1.7
Coffee* + cola + energy drink	2	0.5	-		2	0.8	0	0.0
Coffee* + tea + cola + energy drink	16	4.1	-	58.2	15	6.3	1	1.7
Tea only	53	13.5	46	26.6	-		-	
Tea + cola	23	5.9	21	0.0	-		-	
Tea + energy drink	0	0.0	0	1.3	-		-	
Tea + cola + energy drink	1	0.3	1	10.1	-		-	
Cola only	8	2.0	8	1.3	-		-	
Cola + energy drink	1	0.3	1	0.0	-		-	
Energy drink only	0	0.0	0	2.5	-		-	

*includes decaffeinated coffee

5.4.8 Views about coffee consumption and health

Table 35 presents data that includes participant views about coffee and health and changes to their coffee consumption due to their liver conditions, by coffee drinking status. Tables presenting the data by gender and liver stiffness group, by age group, and by NHS site are available in appendix Q.

There were 228 (76%) of participants who had not changed their coffee drinking behaviour since having their liver condition diagnosed and if they had changed slightly more participants had increased their coffee consumption (41 (14%)) rather than reduced it (31 (11%)).

Most participants had not been given any specific advice about their coffee drinking and if they had it was more likely that it was to drink more coffee than to drink less. Compared to the lower liver stiffness group, a higher proportion of participants in the middle and most severe liver stiffness groups had been advised to drink more.

Among those who were consuming more coffee since their liver condition, 77% had been given that advice by a healthcare professional, and 36% among those drinking less. Only two participants had been given conflicting advice to both drink more coffee and less coffee, although there was no specific option on the questionnaire for this response, and these participants had ticked both options.

The effect of coffee drinking on general health and liver health was something most participants were uncertain. For general health, 174 (45%) of all participants were uncertain. For those who had a specific view, there was a marked difference between current non-coffee drinkers and coffee drinkers with only 3 (4%) of non-coffee drinkers believing coffee to be healthy compared to 72 (24%) of coffee drinkers. Uncertainty about general health effects of coffee also tended to increase with age with a lower proportion of older participants having a view that coffee was beneficial for general health.

Similarly, 223 (58%) of participants were uncertain about the effect of coffee on liver health, with 59 (15%) having a view that coffee was beneficial to the liver and 23 (6%) harmful. Among non-coffee drinkers 3 (4%) felt coffee was beneficial to liver health compared to 56 (19%) of current coffee drinkers.

Table 35: Views about coffee consumption and health by coffee drinking status

		Total sample		Non-coffee drinker		Any coffee-drinker		Caffeinated coffee-drinker		Decaffeinated coffee-drinker	
		N	%	N	%	N	%	N	%	N	%
Coffee drinking changed since the liver condition (n=300)	A lot less	-	-	-	-	17	5.7	10	4.0	7	15.2
	Slightly less	-	-	-	-	14	4.7	9	3.6	5	10.9
	Not changed	-	-	-	-	228	76.0	198	78.6	29	63.0
	Slightly more	-	-	-	-	31	10.3	26	10.3	4	8.7
	A lot more	-	-	-	-	10	3.3	9	3.6	1	2.2
Healthcare professional advice to change coffee intake	No	-	-	-	-	260	85.5	218	85.5	39	84.8
	Drink less	-	-	-	-	11	3.6	10	3.9	1	2.2
	Drink more	-	-	-	-	31	10.2	26	10.2	5	10.9
	Less & More	-	-	-	-	2	0.7	1	0.4	1	2.2
View about coffee and general health	Very beneficial	16	4.1	0	0	16	5.3	14	5.5	2	4.3
	Beneficial	59	15.2	3	3.6	56	18.5	50	19.7	6	13.0
	No effect	84	21.7	10	11.9	74	24.4	61	24.0	13	28.3
	Harmful	49	12.7	11	13.1	38	12.5	33	13.0	5	10.9
	Very harmful	5	1.3	3	3.6	2	0.7	2	0.8	0	0
	Unsure	174	45.0	57	67.9	117	38.6	94	37.0	20	43.5
View about coffee and liver health	Very beneficial	15	3.9	0	0	15	5.0	11	4.4	4	8.7
	Beneficial	44	11.4	3	3.6	41	13.6	38	15.1	3	6.5
	No effect	80	20.8	10	11.9	70	23.3	60	23.8	10	21.7
	Harmful	23	6.0	5	6.0	18	6.0	14	5.6	4	8.7
	Very harmful	0	0	0	0	0	0	0	0	0	0
	Unsure	223	57.9	66	78.6	157	52.2	129	51.2	25	54.3

There was a very clear difference across NHS sites with respect to changes in coffee consumption, healthcare professional advice, and views about general and liver health. A much higher proportion of participants (39%) recruited from the Royal Infirmary of Edinburgh had been consuming more coffee since having their liver condition compared to University Hospital Southampton (9%) and Queen Alexandra Hospital Portsmouth (5%), were much more likely to have been advised to drink more (44% versus <2%) and were much more likely to have a view that coffee was beneficially to both general and liver health, compared to participants from other sites.

5.4.9 Achievability of drinking more coffee

Table 36 presents data on participant views about their capacity for drinking more coffee by coffee drinking status. Tables presenting the data by gender and liver stiffness group, by age group, by NHS site, and by additional subgroups are available in appendix R. Overall 302 (79%) participants agreed that drinking two more cups of caffeinated coffee would be achievable if advised by a healthcare professional including. An *a priori* hypothesis was that a higher proportion of current coffee drinkers would feel able to achieve a two cups a day increase in coffee consumption compared to non-coffee drinkers. There were 87% of current coffee drinkers who felt that the increase was achievable but only 49% of non-coffee drinkers (difference in proportion = 38% (95% CI 27 to 49%, p<0.001)).

For those who did not agree that drinking two more cups was achievable, the main reasons among non-coffee drinkers were dislike of the taste of coffee (55% of all reasons), headaches (10%), sleep being affected (9%), using the toilet too much (9%), and generally feeling unwell (9%). Among current coffee drinkers, the main reasons were an even split between sleep and toileting being affected. A higher proportion of males compared to females felt that drinking an additional two cups of coffee was achievable. Free-text 'other' reasons are available in appendix S.

There were 297 (78%) participants who agreed that they could drink two additional cups of decaffeinated coffee each day if advised by a healthcare professional. Slightly more non-coffee drinkers agreed that this was achievable than when asked about caffeinated coffee. There were no clear differences across NHS sites.

Table 36: Views about achievability of drinking more coffee by coffee drinking status

		Total sample		Non-coffee drinker		Any coffee-drinker		Caffeinated coffee-drinker		Decaffeinated coffee-drinker	
		N	%	N	%	N		N	%	N	%
Could achieve drinking 2 more cups caffeinated coffee if advised by health professional	Yes	302	78.9	41	48.8	261	87.3	227	90.4	32	71.1
	No	80	20.9	42	50.0	38	12.7	24	9.6	13	28.9
	Not sure	1	0.3	1	1.2	0	0	0	0	0	0
Reasons for not being able to drink more caffeinated coffee	Expense	4	3.8	2	3.4	2	4.3	1	3.3	0	0.0
	Time	2	1.9	0	0.0	2	4.3	2	6.7	0	0.0
	Taste	34	32.1	32	55.2	2	4.3	2	6.7	0	0.0
	Sleep	16	15.1	5	8.6	11	23.4	8	26.7	3	18.8
	Unwell	7	6.6	5	8.6	2	4.3	1	3.3	1	6.3
	Heart racing	6	5.7	1	1.7	5	10.6	2	6.7	3	18.8
	Headache	11	10.4	6	10.3	5	10.6	2	6.7	3	18.8
	Anxiety	5	4.7	1	1.7	3	6.4	3	10.0	0	0.0
	Tremor	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Toilet	16	15.1	5	8.6	11	23.4	6	20.0	5	31.3
	Dehydration	5	4.7	1	1.7	4	8.5	3	10.0	1	6.3
Could achieve drinking 2 more cups decaffeinated coffee if advised by a health professional	Yes	297	78.4	45	54.2	252	85.1	212	85.1	38	86.4
	No	78	20.6	37	44.6	41	13.9	35	14.1	5	11.4
	Not sure	4	1.1	1	1.2	3	1.0	2	0.8	1	2.3

5.4.10 Views about future research acceptability, design, and assistance

5.4.10.1 Acceptability

Table 37 presents data on views about the acceptability, design, and assistance required in a future randomised controlled trial for the overall sample and by coffee drinking status. Tables by gender, liver stiffness, and age group are available in appendix T. Overall, 331 (86%) participants felt that the intervention of drinking two extra cups a day was acceptable. A similar pattern was seen for the acceptability of having equal chance of ending up in either group with 319 (83%) of the entire sample agreeing acceptability. There was less variability in the acceptability for tests and scans needed as part of the experimental study across coffee drinking status with 348 (90%) agreeing to the acceptability of both.

5.4.10.2 Nature of the extra coffee in an experimental study

Participants were encouraged to choose all acceptable options for how the extra coffee in a research study should be managed and 233 (59%) of participants selected their own coffee at their own expense, 106 (27%) a fixed allowance, 105 (27%) to be supplied instant coffee, 55 (14%) to be supplied freshly ground coffee and a suitable device to prepare it, and 36 (9%) expressed uncertainty.

There were 262 participants who chose only one option, of which 152 (58%) were keen to drink their own coffee at their own expense, 35 (13%) preferred a fixed allowance to put towards the financial cost of the coffee, 32 (12%) preferred to be given the actual coffee in the form of instant, and 10 (4%) in the form of ground coffee with a suitable preparation device. This left 32 (12%) participants who remained unsure as to the best way for the coffee to be organised. Among those choosing their own coffee as their only option, 64% had instant coffee as one of their regular preparation types, and for 61% of these, instant was the only coffee type they consumed on a regular basis.

5.4.10.3 Assistance

Most participants did not feel any additional help was needed to remember to take an additional two cups of coffee a day in a research study with 239 (65%) of participants selecting this option. However, 109 (30%) selected text messages as a useful option.

5.4.10.4 Participation in a future study

Overall 272 (72%) of participants agreed, hypothetically, that they would be interested in participating in this type of experimental study. An *a priori* hypothesis was that non-coffee drinkers would be less likely to be interested in taking part in the proposed future randomised controlled trial than coffee drinkers. A higher proportion of those currently drinking coffee (78%) expressed a hypothetical interest in participation compared with those not currently drinking any coffee (51%), (difference in proportion 27% (95% CI 15 to 38%, p=<0.001)). A lower proportion of decaffeinated coffee drinkers expressed an interest in participating in a future study compared to caffeinated coffee drinkers. Hypothetical interest in taking part in a future research study by additional subgroups is also shown in appendix T. Free text reasons for not being interested in participating in a future randomised controlled trial are available in appendix U.

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Table 37: Research acceptability, design, and assistance by coffee drinking status

Characteristic		Total sample		Non-coffee drinker		Any coffee-drinker		Caffeinated coffee-drinker		Decaffeinated coffee-drinker	
		N	%	N	%	N	%	N	%	N	%
Intervention acceptable (2 extra cups of coffee each day versus usual intake)	Yes	331	85.5	65	77.4	266	87.8	229	90.2	36	78.3
	No	26	6.7	12	14.3	14	4.6	10	3.3	3	6.5
	Not sure	30	7.8	7	8.3	23	7.6	15	5.9	7	15.2
Randomisation acceptable (Equal chance of ending up in each group)	Yes	319	82.6	63	75.0	256	84.8	219	86.6	35	76.1
	No	28	7.3	11	13.1	17	5.6	13	5.1	4	8.7
	Not sure	39	10.1	10	11.9	29	9.6	21	8.3	7	15.2
Blood tests acceptable	Yes	348	90.4	75	90.4	273	90.4	230	90.9	41	89.1
	No	20	5.2	3	3.6	17	5.6	16	6.3	1	2.2
	Not sure	17	4.5	5	6.0	12	4.0	7	2.8	4	8.7
Liver scans acceptable	Yes	349	90.6	74	89.2	275	91.1	230	90.9	43	93.5
	No	17	4.4	3	3.6	14	4.6	14	5.5	0	0
	Not sure	19	4.9	6	7.2	13	4.3	9	3.6	3	6.5
How should the extra coffee be organised for the intervention group?	Own coffee	233	43.6	38	38.4	195	44.7	166	44.6	29	46.8
	Allowance	106	19.8	18	18.2	88	20.2	77	20.7	10	16.1
	Instant	105	19.6	21	21.2	84	19.3	70	18.8	14	22.6
	Ground	55	10.3	8	8.1	47	10.8	42	11.3	5	8.1
	Not sure	36	6.7	14	14.1	22	5.0	17	4.6	4	6.5
	Other										
Help needed to remember to take extra coffee in a research study	None	239	64.8	49	63.6	190	65.1	156	62.7	33	78.6
	Texts	109	29.5	23	29.9	86	29.5	79	31.7	7	16.7
	Emails	7	1.9	2	2.6	5	1.7	4	1.6	1	2.4
	Texts+email	8	2.2	1	1.3	7	2.4	6	2.4	1	2.4
	Other	6	1.5	2	2.6	4	1.4	4	1.6	0	0
Would you be interested in taking part in this type of study?	Yes	272	72.0	43	51.2	229	77.9	200	80.0	29	67.4
	No	56	14.8	29	34.5	27	9.2	23	9.2	4	9.3
	Not sure	50	13.2	12	14.3	38	12.9	27	10.8	10	23.3

5.4.10.5 Achievability of drinking more coffee and participating in the research

Table 38 presents the proportion of participants that agreed to the achievability of drinking two additional cups of caffeinated coffee, and participants agreeing to achievability and interest in participation, by liver stiffness group and baseline coffee consumption. It also presents the proportion who did not agree to the achievability of drinking two additional cups of caffeinated coffee, but not because of taste, and who consumed other caffeinated beverages, a group that potentially could use substitution between beverages to achieve the outcome.

Overall 41 (47%) non-coffee drinkers, and 205 (85%) of 1-3 cups a day drinkers felt drinking more caffeinated coffee was achievable, reduced to 33 (38%) and 159 (66%) respectively when adjusted for those also expressing a hypothetical interest in taking part. Acceptable interventions for these participants were own coffee (70%), allowance (30%), given instant, given ground coffee or unsure (3% each) among non-coffee drinkers, and own coffee (70%), allowance (26%), given instant (31%), given ground coffee (14%) and unsure (5%) among 1-3 cup consumers.

Approximately 9 (10%) of non-coffee drinkers and 18 (8%) of 1-3 cups a day drinkers, did not think drinking more caffeinated coffee was achievable, but not because of the taste, and also consumed other caffeinated beverages, opening a potential window for substitution.

Table 39 presents the same data for only those participants with an AUDIT-C score of <5 (lower risk alcohol intake). Results were similar across subgroups of these participants of lower alcohol intake.

Table 38: Achievability of drinking more coffee and interest in taking part in the research by coffee cups a day and liver stiffness (KPa)

	Participants drinking 0 cups/day								Participants drinking 1-3 cups/day							
	All		Liver stiffness						All		Liver stiffness					
			<7KPa		7-13KPa		>13 KPa				<7KPa		7-13KPa		>13 KPa	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Would achieve drinking 2 more cups of caffeinated coffee	41	46.6	9	40.9	14	41.2	18	56.3	205	85.4	77	78.6	81	94.2	47	85.5
Would achieve drinking 2 more cups of caffeinated coffee and would be interested in taking part in a future randomised controlled trial	33	37.5	7	31.8	13	38.2	13	40.6	159	66.3	59	60.2	64	74.4	36	65.5
Would not drink 2 more cups of caffeinated coffee, but not because dislike of taste; consumes caffeinated tea, cola or energy drink	9	10.2	3	13.6	4	11.8	2	6.3	18	7.5	9	9.2	4	4.7	4	7.3

Table 39: Achievability of drinking more coffee and interest in taking part in the research by coffee cups a day and liver stiffness (KPa) in participants with AUDIT-C score <5

	Participants drinking 0 cups/day								Participants drinking 1-3 cups/day							
	All		Liver stiffness						All		Liver stiffness					
			<7KPa		7-13KPa		>13 KPa				<7KPa		7-13KPa		>13 KPa	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Would achieve drinking 2 more cups of caffeinated coffee	32	45.7	7	43.8	8	32.0	17	58.6	144	85.2	50	78.1	55	93.2	39	84.8
Would achieve drinking 2 more cups of caffeinated coffee and would be interested in taking part in a future randomised controlled trial	27	38.6	6	37.5	8	32.0	13	44.8	110	66.2	38	59.4	42	71.2	30	65.2
Would not drink 2 more cups of caffeinated coffee, but not because dislike of taste; consumes caffeinated tea, cola or energy drink	8	11.4	3	18.8	3	12.0	2	6.9	14	7.4	7	10.9	3	5.1	4	8.7

5.5 Discussion

The CUPLID cross-sectional survey was conducted across three NHS hepatology units and a total of 688 patients with NAFLD were invited to take part. The questionnaire was returned by 393 participants giving a return rate of 57%, and included 305 coffee drinkers (78%) and 88 non-coffee drinkers (22%). There are several findings from the survey that address the research objectives and provide important knowledge to help plan the next steps towards a randomised controlled trial in which coffee is tested as a treatment for established fatty liver disease.

Participants can be divided into three distinct groups – those that currently consume no coffee (0 cups a day), those drinking 1-3 cups a day, and those drinking ≥4 cups a day. Arguably, only those drinking, 0 or 1-3 cups a day may derive a benefit from drinking more, whereas those consuming ≥4 cups a day would be considered to have already passed an intake threshold. In the CUPLID survey, 22% consumed 0 cups a day, 61% consumed 1-3 cups a day, and 17% consumed ≥4 cups a day. Thus a total of 83% of participants could potentially benefit from increasing their coffee consumption in a scenario in which coffee intake had proven benefit in NAFLD. Reassuringly, the majority of coffee consumed could be considered healthy, with lower fat milk options and only the minority adding sugar.

The next consideration is how many participants think they could achieve an increase of coffee, or starting to drink it, if advised by a healthcare professional. This is important because irrespective of any evidence from a future trial, if patients thought drinking more coffee was unachievable, then any benefit from drinking more may never be realised. In the CUPLID survey, 47% of non-coffee drinkers and 85% of 1-3 cups a day drinkers felt that starting, or increasing, caffeinated coffee consumption of two cups a day, would be achievable. Overall this represents 63% of all participants.

However, when considering the proportion of participants within this group who also expressed an interest in taking part in this type of research the overall proportion drops to 49% of all participants. So in summary, approximately half of all participants could potentially benefit from drinking more coffee based on their baseline intake, thought that increasing consumption was achievable, and expressed a hypothetical interest in taking part in this type of study.

However, further consideration needs to be given to which type of NAFLD patients would be likely to benefit from such an intervention. For changes to be detectable within the time frame of a randomised controlled trial, for example by the use of biomarkers, imaging or histology, patients will need to have advanced along the NAFLD pathological pathway, with significant fibrosis or cirrhosis. As such particular interest would be in patients in liver stiffness group 2 (≥7 to ≤13 kPa) and 3 (>13 kPa), and excluding liver stiffness group 1 participants from the projections above, reduces the total proportion who may be eligible to 32%. The flow of participants through this possible recruitment sieve is shown diagrammatically in Figure 40, which also shows the proportion of the final 32% of the sample drinking 0 or 1-3 cups a day, and the proportion of each of those sub-groups who selected from the choice of possible ways of organising the extra coffee in an experimental study. Most of these participants found being asked to drink their own coffee at their own expense an acceptable method.

Generally the research plans were viewed as acceptable, including being randomised between usual coffee and increased coffee intake, having blood tests and scans, and there were no major differences across liver stiffness groups, or across categories of coffee drinkers.

A step further is to consider the coffee unit intake. As discussed in chapter 3, one coffee unit is equivalent to 227 mL (8oz) of instant coffee and is based on the caffeine and chlorogenic acid content. Coffee unit estimation was made for each participant's intake of coffee consumed the day before they completed the survey. Whilst no target coffee intake has been established based on cups or coffee units, the coffee unit measure provides the advantage of taking into account cup size and preparation type. As such a starting point for considering who may benefit amongst current coffee drinkers may be those consuming <4 coffee units a day, although in a future study cups a day, rather than units, may be the preferred measure since the observational research has been based on this. Misclassification between reported cups and coffee unit standardised cups occurred in 52% of participants, mostly underestimating intake by 1 or 2 cups a day. This means that a number of participants would probably move from the 1-3 cups a day group to a ≥4 standardised cups a day group were coffee units to be the preferred measure. However, some, among the few with overestimated intake, may move in the other direction if drinking decaffeinated coffee or smaller than average cup sizes.

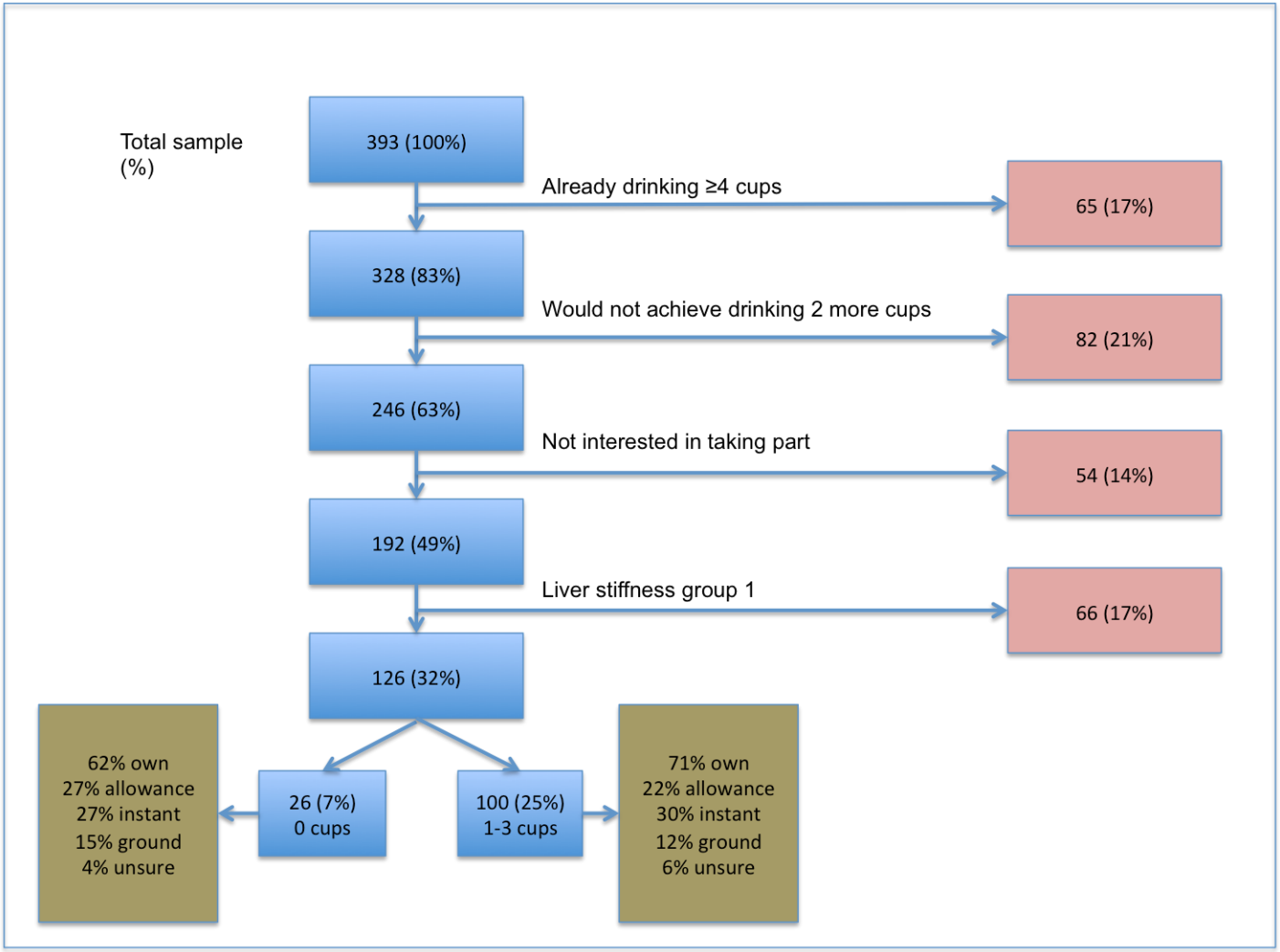


Figure 40: Flow of possible eligibility/interest in participation in a future RCT

People consuming no coffee at all on a regular basis are likely to be a different group than modest coffee drinkers with respect to achieving an increase in coffee consumption, a hypothesis that is corroborated by the survey findings. However, reassuringly as described above, a reasonable proportion of non-coffee drinking participants agreed to the achievability of starting to drink two cups of caffeinated coffee, an interest in taking part in the research, or both. For many non-coffee drinkers, an aversion to the taste of coffee was the main reason for not being able to drink it. For these people with NAFLD starting to drink coffee may not be achievable despite potential benefit to their liver health. Free-text comments corroborate the strength of dislike towards the taste of coffee.

There were also a group of participants who were identified as potentially being able to drink more caffeinated coffee through substitution despite negating the achievability of drinking two cups of caffeinated coffee, since they also consumed non-coffee caffeine across the spectrum of tea, cola or energy drink. These participants were divided between those who had selected taste as the reason they could not drink coffee/more coffee and those that had not. Those that were not put off by taste, could potentially use substitution to increase coffee intake, and negate any undesirable effects of excess caffeine, such as insomnia or frequency of urination, by limiting the overall exposure. As discussed in chapter 1, coffee caffeine may have a synergistic relationship with other compounds within coffee, and coffee caffeine in preference to non-coffee caffeine may offer greater benefit to the liver. Clearly any future experimental study will need to quantify all non-coffee caffeine consumed and adjust results accordingly.

The CUPLID survey targeted patients with NAFLD. NAFLD is a clinical diagnosis and diagnostic criteria, although vary slightly from guideline to guideline, generally exclude significant alcohol intake. The definition of alcohol intake used in NAFLD does vary as described in chapter 1. The use of the AUDIT-C questionnaire in the CUPLID survey was a simple way to assess alcohol intake and 27% of the entire sample scored ≥5, a score that would normally trigger the full AUDIT questionnaire. As such it could be assumed that about a quarter of the sample are not a pure NAFLD group, and the aetiology of their fatty liver condition could include alcohol. This may be a similar issue with inclusion criteria for a future treatment study, and possibly a reflection of the real world, where pure NAFLD may be less frequent than the diagnostic label might suggest. As discussed in chapter 1, coffee may also be beneficial in reducing the risk of alcohol-related liver damage, such that a BAFLD group may also benefit. Participants with an AUDIT-C score <5 were not obviously different than the complete sample with respect to achievability of drinking more coffee, and when combined with interest in taking part.

An important part of considering a future randomised controlled trial is clinical equipoise, which must still be present to make such a trial worthwhile, and remain ethically appropriate. The majority of participants had not been advised to drink more coffee by any of their healthcare professionals, across any of the three NHS sites. However, there was a clear difference between participants from Edinburgh and elsewhere with 44% of participants having been advised to drink more in Edinburgh, compared to <2% in other sites. Coffee and liver health have been of specific interest to a number of consultant hepatologists in Edinburgh Royal Infirmary for many years and it is not surprising that advice may have been given to NAFLD patients to drink more coffee. However, even in this environment half the patients had not been given this advice despite attending the outpatient department and arguably therefore clinical equipoise still exists at this site too. Recent guidance from the European Society for the Study of Liver Disease (EASL) for reducing the risk of HCC in people with chronic liver disease, has included coffee as a strong recommendation[283], but with only moderate evidence. Considered together, there may be a gradual shift in clinicians towards acceptance of coffee as beneficial for liver health, but a window of opportunity remains to confirm a causative benefit by conducting a randomised controlled trial in patients with NAFLD.

5.5.1 Strengths and limitations

The CUPLID survey has offered a unique insight into coffee drinking behaviour in a sample of people with NAFLD living in the UK, and important new knowledge about views on achievability of increasing coffee intake, and about acceptability of intervention, design and assistance in a proposed future randomised controlled trial. A key strength of the survey is the high return rate and the sample size target being achieved. The sample size calculation was based on one key question about achievability of drinking two additional cups of coffee a day if advised by a healthcare professional, and anticipated differences between current coffee and non-coffee drinkers in this response. The two *a priori* hypotheses arguably offer no intrinsic value other than to appreciate that differences do exist between those of different coffee drinking status. No other specific comparisons between groups were planned *a priori*, and the strength of the survey is in the volume of descriptive data available. Indeed specifically no *a priori* hypothesis testing was planned to assess differences in coffee drinking between the three liver stiffness groups although

the proportion of coffee drinkers versus non-coffee drinkers did reduce as liver stiffness increased, which appears to be consistent with the existing literature suggesting coffee may reduce the risk of fibrosis and cirrhosis. The number of coffee cups/units a day among those drinking coffee did not differ between liver stiffness groups except when stratifying further by alcohol intake. This revealed that those with lower alcohol intake and higher liver stiffness consumed less coffee than those with higher alcohol intake or lower liver stiffness. A limitation of the survey is the omission of historic coffee drinking data. Whilst the qualitative component suggested reasonable stability of intake over time, the questionnaire could have asked non-coffee drinkers whether they had ever regularly consumed coffee. Only participants who were regular coffee drinkers were asked whether they drank more coffee or less coffee since they have had their liver condition, and most had not changed. However, it is possible that a proportion of current non-coffee drinkers may have previously consumed coffee, and the questionnaire has not captured this additional information. However, some studies suggest little change in coffee consumption even amongst those with advanced cirrhosis[67].

A further strength of the survey is that the sample was well represented across a range of NAFLD severity, gender and age, with only apparently small differences between participants and non-participants for these characteristics. Participants were slightly older, had a slightly higher male:female ratio, and slightly skewed towards less severe liver stiffness when compared to non-participants. One limitation is the lack of other characteristics to compare participants and non-participants in order to know how representative the sample was. It is possible that the prevalence of coffee drinking in the sample was higher than in the general NAFLD population because coffee drinking patients were perhaps more likely attracted to taking part in research about coffee, although non-coffee drinkers were strongly encouraged to participate, and 22% of the sample were non-coffee drinkers. Reassuringly, the prevalence of non-coffee drinking is very similar to that within the UK Biobank, but lower than the prevalence of non-coffee drinking in the NDNS sample (chapter 3). However, the latter may not reflect true coffee drinking prevalence because the data was derived from 4-day food diaries that may have missed less frequent consumption.

Another strength of the survey was the level of detail obtained about coffee drinking. The main quantification data came from coffee consumed ‘yesterday’. This had the advantage of limiting recall bias among participants, since details of the day before consumption should be fresh in the minds of participants, but only 274/305 coffee drinkers consumed coffee the day before. The coffee unit estimates were also based on this data since the questionnaire aimed to capture the size and preparation types of all coffee consumed.

The day before consumption was still prone to some misclassification due to patients selecting the cup size from the list of options, rather than actually measuring the volume of the vessel used, although the preparation type data should be more accurate. Indeed the classification of coffee type is arguably more detailed than that used in the NDNS, especially for those termed 'infusions' in the NDNS and probably included filter, cafetière, and capsule/pod coffee, all of which were separate selections in the CUPLID survey. Further misclassification is possible due to differences in types of actual coffee used, degree of roasting, number of spoons of instant coffee used etc.

A limitation in the sample is the ability to generalise the findings across ethnicities. Most respondents in our survey were white and the sample is likely to under-represent black and minority ethnic groups. In the 2011 Census for England and Wales, Scotland and Northern Ireland, the prevalence of the white population was 87%, slightly lower than the 92% in the CUPLID survey. This may be a reflection of the local population with respect to two south coastal populations, and one in Scotland. However, NAFLD prevalence may also be higher in some Asian ethnic groups, such as those of Bangladeshi origin, since metabolic syndrome is common in people of South Asian origin, and this has known associations with NAFLD[284]. The prevalence of smoking in participants (8%) was also lower than the national average (15%). Cigarette smoke is now recognised as a risk factor for NAFLD[285], and patients who smoke may also be under-represented in the CUPLID survey. Some patients may have quit smoking but this data was not collected in the survey.

A further limitation of the survey was absence of data on non-coffee caffeine consumed the day before the questionnaire was completed. In the early drafts of the questionnaire, more detailed information on every beverage consumed the day before the questionnaire was included, but the overall survey instrument was felt too long and cumbersome, with a risk of not being able to engage participants. The excellent return rate in the final survey was testament to a usable instrument that could be completed with relative ease and in a short time frame, estimated to be 10-15 minutes. More detailed information about non-caffeine consumption might also have helped generate more insight into the potential for substitution. The sub-theme of substitution arose in the qualitative phase of CUPLID and the questionnaire could also have benefitted from specifically asking whether participants would be willing to substitute non-coffee caffeinated beverages for coffee, especially in those who felt that they could not start, or increase coffee consumption, for reasons other than taste. A large proportion of participants consumed coffee and other non-coffee

caffeinated beverages, especially tea, and substitution offers a real possibility to increase capacity for drinking coffee, but the concept would need to be tested.

5.6 Conclusion

The quantitative, survey phase, of CUPLID has provided insight into coffee drinking behaviour amongst a secondary care population of people with NAFLD. It has suggested that approximately 50% of NAFLD patients would be drinking coffee at a baseline where increased consumption might offer benefit to liver health, and who agreed to the achievability of that increase, and who would be hypothetically interested in taking part. This proportion drops to 32% in a scenario where only those with more severe liver stiffness would be eligible. Whilst this is about a third of total respondents, it is encouraging that recruitment into an experimental study is likely to be achievable form a general NAFLD population attending outpatient hepatology clinics in a secondary care setting.

Chapter 6: Summary of findings and discussion

6.1.1 Introduction

Within the body of work contained within chapters 1 to 5 of this thesis I have:

- Summarised existing studies between coffee drinking and liver health outcomes
- Assessed the evidence for the association between coffee drinking and multiple health outcomes including an assessment of the quality of this evidence
- Developed a new coffee unit measure and applied this to both a general and NAFLD population to estimate misclassification in coffee intake when preparation type and cup size are unaccounted for
- Conducted a mixed methods study in people with NAFLD to explore patterns of coffee consumption, views about achievability of drinking more coffee, and acceptability of further coffee research, by using a combination of semi-structured interviews, and a survey

This final chapter:

- Summarises the main findings of the body of work in this thesis
- Briefly summarises the significance of NAFLD and coffee
- Describes a rationale for an RCT and discusses Mendelian Randomisation studies
- Discusses:
    - A target for coffee intake in a future RCT
    - The use of a coffee unit measure in coffee investigation
    - Nature of a coffee intervention
    - Decaffeinated coffee
    - Behavioural change in a coffee RCT
    - Eligibility for participation in a future RCT
- Highlights key strengths and limitations in the body of work
- Summarises recommendations and next steps

6.1.2 Main findings

<u>Literature review</u>

- The association between coffee intake and liver outcomes has been the subject of scientific enquiry since the early 1990s

- There appears to be consistent beneficial associations with a lower risk of liver fibrosis, cirrhosis, and hepatocellular carcinoma, but nearly all this evidence comes from observational research challenged by various bias and confounding issues
- Most coffee and liver research does not focus on NAFLD but fibrosis, cirrhosis and hepatocellular carcinoma are common sequelae of chronic insult to the liver from any aetiology
- There is a robust biological plausibility in the beneficial effect between coffee consumption and liver health including a reduced risk of fat accumulation, reduced hepatic stellate cell activity leading to reduced fibrogenesis, and reduced oxidative stress and inflammation

Coffee umbrella review

- Aside from harms in pregnancy and higher risk of fracture in women, coffee does not appear to be associated with any harmful outcomes, and reassuringly appears to be beneficially associated with generic outcomes of all-cause mortality, cardiovascular mortality, and total cancer
- The magnitude of the beneficial effect between coffee consumption and liver outcomes is consistently larger than those seen in other beneficial associations for other health outcomes

Development of a coffee unit measure and assessment of misclassification

- A recurring issue in studies of coffee consumption and health outcomes to date is the use of the coffee cup as a measure of exposure which risks significant misclassification and shown to effect 1 in 4 participants in the NDNS, and 1 in 2 participants in a survey of patients with NAFLD recruited from secondary care
- Misclassification was higher in men, younger adults, and people with higher incomes
- Misclassification appears to be more commonly underestimate intake due to larger cups, or consumption of coffee types with higher concentrations of caffeine and chlorogenic acids
- The effect of this misclassification on observational research to date is uncertain – it is likely to be non-differential and therefore dilute the risk estimates of benefit and harm
- This coffee unit measure could be used in a randomised controlled trial to better classify baseline coffee intake or to guide an intervention in a free-living pragmatic design where people can consume their preferred coffee type

Mixed methods study of coffee drinking in people with NAFLD

- Themes arising from the thematic analysis of qualitative data from 17 semi-structured interviews suggest that a patient with NAFLD would be more likely to increase their *baseline regular intake* if they have the enabling capacity, motivation, opportunity and flexibility
- A survey of 393 patients with NAFLD recruited from secondary care revealed:
    - 22% drank no coffee
    - 61% consumed 1-3 cups/day
    - 17% consumed >= 4 cups/day
- This suggests that approximately 4 in every 5 patients with NAFLD could potentially benefit from drinking more coffee should it have proven efficacy as a treatment for NAFLD and were we to use an upper limit of 4 cups/day
- This proportion of coffee drinkers amongst NAFLD patients is similar to the general population, but the proportion of coffee drinkers decreased as NAFLD severity increased
- 47% of non-coffee drinkers felt that they would be able to commence caffeinated coffee consumption (of 2 cups/day) if it was shown to have benefits for the health of their liver; 85% of those consuming 1-3 cups/day felt they would also be able to increase consumption by 2 cups/day
- These proportions reduced to 38% and 66% respectively when excluding those who would not be interested in participating in a randomised controlled trial
- Aspects of a randomised controlled trial including coffee as an intervention, randomisation, and blood tests and liver scans were felt acceptable by most participants
- 64% of participants felt that no additional help would be needed in a randomised controlled trial to remember to drink additional coffee; 30% felt text messaging reminders could be useful
- Most participants had <u>not</u> been advised to drink coffee by their hospital clinician and this suggests that clinical equipoise still exists
- An additional 10% of non-coffee drinking participants, who felt unable to consume 2 cups/day caffeinated coffee, consumed non-coffee caffeinated drinks and did not cite taste as the reason for not consuming coffee. This suggests a possible role for substitution as a method of introducing coffee. This was also the case for an additional 8% of 1-3 cups/day coffee drinkers

- This data suggests that it should be possible to recruit sufficient patients with NAFLD from a secondary care setting into a randomised controlled trial in which coffee is tested as an intervention

6.1.3 NAFLD and coffee

In chapter 1, the high burden of liver disease in the UK was introduced, setting the context for this important public health problem, and existing evidence from studies investigating coffee intake and NAFLD were described. Coffee has been associated with reduced risk of Non-Alcoholic Steatohepatitis, fibrosis, cirrhosis and hepatocellular carcinoma. Associations between coffee intake and the first stage of NAFLD, steatosis, have been less convincing. Irrespective of aetiology, the chronic insult to the liver leads to the common pathological processes of fibrosis, cirrhosis, and HCC. Approximately a third of patients who participated in the survey conducted as part of this thesis self-reported alcohol consumption that would be classified as higher risk using the validated Audit-C score. This group would be classified as BAFLD – Both Alcohol and Fatty Liver Disease recognised as a group where alcohol and fat both play a role in development of liver disease. Existing observational evidence suggests that coffee may also mitigate some of the damaging effects of alcohol.

Coffee is consumed on a massive scale, with 95 million cups consumed each day in the UK[17]. Approximately 80% of the general population consumes coffee on a regular basis[275], and new research presented in this thesis has shown a similar proportion of coffee drinkers amongst patients with NAFLD. Coffee, essentially the dried, roasted and ground product of the fruit from the coffee tree, comprises of over 1000 bioactive compounds. Many of these compounds exert biochemical affects in various liver processes, and biological plausibility for coffee's benefit in NAFLD include a reduced risk of fat accumulation, reduced hepatic stellate cell activity leading to reduced fibrogenesis, and reduced oxidative stress and inflammation[56,111]. However, simple steatosis is largely a quiescent condition, with only a small proportion of patients advancing along the pathological pathway towards fibrosis. NASH is a stage characterised by inflammation, hepatic ballooning, and often associated with additional oxidative stress. As coffee is a significant dietary contributor of antioxidant compounds, it may be most beneficial when additional stressors do exist. Indeed coffee has been shown to reduce the risk of

advancing liver pathology in relation to both alcohol related liver disease[67], and in Hepatitis C infection[286]. However, the potential for coffee to counteract oxidative stress may be limited when there are very damaging oxidative processes involved. For example, coffee was only shown to be beneficially associated with liver health in patients with low but not high insulin resistance[63].

6.1.4 Rationale for needing an RCT

As discussed in chapter 1, most of the existing evidence between coffee and liver outcomes come from observational studies, including cross-sectional, case-control, and cohort studies. Each of these has limitations and risk several types of bias. Risk of confounding is one major limitation common to all observational studies. This is where a known or unknown risk factor is unaccounted for in the observations made, leading to spurious associations between an exposure and outcome. Randomised controlled trials (RCTs) circumvent the risk of confounding if true random allocation is achieved, and if the trial is of sufficient size, where confounding factors are equally distributed between the intervention and the control groups. Differences between the two groups are more likely to result from the intervention than due to some other factor, but RCTs should be critically appraised in their own right, since no form of study is free from risk of error or bias. Importantly, no RCTs have been published to date to investigate the effect of coffee intake on clinical liver disease, and specifically NAFLD. Arguably now is the time, in the context of the huge burden NAFLD, the lack of effective treatments, and the potential coffee has to offer benefit.

Mendelian Randomisation may offer another research mechanism to investigate the association between coffee intake and liver health outcomes. In short, this methodology's strength is the natural randomisation of confounders between genotypes of known function related to the specific outcome of interest. The method relies on several assumptions[287]:

1. The genetic variants are associated with the modifiable exposure of interest
2. The genetic variants are not associated with confounders of the exposure to outcomes association

3. The genetic variants only influence the outcome through the exposure of interest and not through another factor

Two MR studies were discussed at the end of chapter 2 between coffee drinking and type II diabetes, and coffee drinking and all-cause mortality, both of which shed doubt on the observational research findings of beneficial associations for both conditions. More recently a Mendelian Randomisation approach has been used to investigate the association between coffee consumption and NAFLD using data from the UK Biobank[288]. The study reported a non-significant trend towards a causal protective effect of coffee intake on NAFLD but the authors concluded that the findings did not support a causal relationship. One key issue with MR studies is how specific the genetic alleles are to coffee consumption. In this recent NAFLD MR study the genetic variants may have been associated with caffeine metabolism, taste and reward-response, rather than coffee consumption per se. In addition to this trait heterogeneity, other issues in MR studies include pleiotropy (where Single Nucleotide Polymorphisms (SNPs) reaching genome-wide significance are strongly associated with other traits as well as the exposure of interest) that can violate the third assumption. Notably, alcohol consumption was found to also be associated with coffee-related genetic variation in another UK Biobank study[289] and this horizontal pleiotropy may explain the lack of significant association in the NAFLD MR study. Collider bias, where both the exposure and outcome can influence a third risk factor that has been adjusted for in the analysis, can also lead to spurious associations between the exposure of interest and the outcome[287]. This is a risk in MR studies investigating coffee exposure and outcomes when non-coffee drinkers are excluded from the analysis with the argument that the SNPs are associated with the degree of coffee drinking and that causal relationships should only be observed among coffee drinkers. However, SNP-associations among non-coffee drinkers would suggest a violation in the first assumption. It should also be noted that the genetic instruments used in MR studies will have been created using GWAS in studies where ascertainment of coffee intake be affected by the same issues of misclassification highlighted in chapter 3 of this thesis. MR studies also assume a linear dose-response relationship and this appears not to be the case for a number of health outcomes. Finally, it should be noted that genetic variation explains <1% of variability in coffee intake[289].

Whilst MR offers some possible insights into the causal associations between coffee and health outcomes, the limitations described above and trend in the NAFLD MR study towards a protective effect, the existence of clinical equipoise, and a strong biological plausibility, mean that an RCT would be an appropriate next step in attempting to prove a causal association between coffee consumption and benefit to NAFLD outcomes.

6.1.5 A target for coffee intake in a future RCT

As previously discussed, there are two groups of patients who may benefit from increased coffee consumption. Firstly, those that drink no coffee at all, and in whom adding coffee into their diets might be beneficial, and secondly, those that drink coffee below a threshold at which coffee might be beneficial, such as those currently drinking 1-3 cups a day. A clue to a possible target coffee intake comes from the observational research suggesting that intakes of 4 cups a day may be associated with a range of benefits. Meta-analyses conducted for coffee and some liver outcomes such as cirrhosis and HCC have suggested a linear dose-response relationship, and arguably higher intakes, beyond 4 cups a day, may deliver higher benefit. However, for other outcomes, as detailed in the coffee umbrella review in chapter 2 and highlighted above, coffee drinking had non-linear associations with some important generic outcomes such as all-cause mortality, cardiovascular mortality, and incident cardiovascular disease, and maximum relative risk reduction was seen at intakes of 3-4 cups a day. Therefore, a threshold intake of 4 cups of coffee a day would seem to be appropriate. Additionally, higher levels of coffee intake, may more likely evoke some undesirable physiological effects of caffeine such as insomnia, urination, headache, palpitations and anxiety, effects that many patients with NAFLD cited as reasons for not being able to increase their coffee consumption when asked in our survey, detailed in chapter 5. Importantly, evidence from the umbrella review in chapter 2, suggests that drinking coffee is more frequently associated with benefit than harm, outside of pregnancy. The umbrella review also revealed an association of coffee drinking with higher fracture risk in women, but not men, and this would need to be carefully monitored in a future RCT in which coffee was given as a treatment, especially because chronic liver disease is known to be associated with increased risk of osteoporosis[290], and any risk to bone health would have to be carefully balanced with benefit to health of the liver.

Reaching a target intake of 4 cups/day may be a challenge for some people. Following the extensive media response to the publication of the coffee umbrella review, hundreds of online comments were collated, many of which described personal accounts of caffeine intolerance, even at much lower cups a day levels than the 3-4 cups suggested by the review. Interindividual differences in caffeine absorption and metabolism are likely to explain some difference in consumption patterns, and linked to the individual experience of physiological (or pathological) effects of caffeine[291]. Polymorphisms of genes for caffeine metabolising enzymes or adenosine receptors may partly explain these individual

differences[291]. Caffeine use disorder, is recognised in the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5), as an entity requiring further evaluation[292]. DSM-5 defines caffeine use disorder as 'a problematic pattern of caffeine use leading to clinically significant impairment or distress' and nine criteria are included of which the first three must be present for diagnosis – these are essentially unsuccessfully cutting down, continued use despite problems, and experience of withdrawal symptoms. Little is known about thresholds of caffeine consumption that could lead to such diagnoses and the majority of coffee drinkers are unlikely to meet these diagnostic criteria. General population prevalence of caffeine use disorder is not fully understood but may be in the region of 10%[293]. In three case studies of caffeine use disorder presented in one article, total daily intake of caffeine from all sources combined was between 498-702mg a day and frequently from non-coffee sources[293]. Depending on the size and contents of a cup, this is likely to be greater than moderate coffee consumption of 3-4 cups a day. Again, interindividual differences between people may make some more susceptible to caffeine withdrawal effects than others. For some, even small amounts of regular caffeine can lead to symptoms of withdrawal that may contribute towards a diagnosis of dependence[294]. Interindividual differences in patients within an RCT, much like confounding factors, would be randomised between intervention and control. In a future RCT, undesirable effects of caffeine would have to be carefully monitored and recorded. This may be especially important among caffeine naïve individuals who may be prone to transient elevation in blood pressure. Genotyping participants for known polymorphisms related to caffeine metabolism may be an important consideration in a future RCT to see if any changes in NAFLD progression due to increasing coffee consumption were specific to the way caffeine was metabolised.

6.1.6 Cups versus coffee units – effects of misclassification

Whilst recognising that the observational research points towards optimal benefit of 3-4 cups of coffee a day, one major issue with coffee intake ascertainment is misclassification, as highlighted in chapter 3. Cups/day is a heterogeneous measure due to differences in preparation type and cup size, type of bean, and coffee roast. In the National Diet and Nutrition Survey data approximately 1 in 4 people had a misclassified intake, largely underestimated, when not taking preparation type and cup size into account. In our CUPLID survey, misclassification affected 1 in 2 participants with NAFLD, with greater underestimation compared to the NDNS, although methodological differences are likely to

account for this difference. The misclassification raises the question as to whether coffee units, rather than coffee cups, should be used as a threshold intake for coffee in a future RCT. Misclassification towards underestimated intake suggests that the proportion of eligible patients below an intake of 4 reported cups a day would be higher than if using 4 standardised cups (units) a day, possibly reducing the proportion of eligible patients from the secondary care NAFLD population if units were used instead of cups.

6.1.7 Nature of the intervention – what type of coffee?

The coffee unit measure also raises the question of what form the intervention should take in a future RCT, and whether any increase in consumption should be measured in units rather than cups. One key advantage of units over cups is that it can be applied across preparation types and therefore has potential to allow participants to drink any type of coffee they wish, as long as they reach a target intake. This gives opportunity for a free-living pragmatic design to be utilised in an RCT. As highlighted in our qualitative analysis, preparation type is an important factor in the motivation for people to drink coffee, and this extends to interest in participating in a future RCT. As such, offering a flexible approach might encourage more patients to participate. However, providing instant coffee appears to be another acceptable approach to the majority of NAFLD patients who drink instant coffee on a regular basis. Instant coffee could be supplied in an RCT, and this was viewed as an acceptable option by 20% of all participants. Instant coffee was also consumed by approximately 60% of those who were happy to drink their own coffee in the context of an RCT suggesting instant coffee provision would fit with many participant's preferences. The qualitative findings suggest that this would need to be of sufficient quality in taste to satisfy some consumers, or alternatively a fixed allowance could be given to participants to purchase their preferred brand. The flexibility of people simply increasing their preferred preparation type or brand of coffee might offer a more generalisable result, which can be applied more easily on a population level, compared to a more medicalised approach, for example prescribing a very specific quantity of instant coffee. However, the more medicalised approach may offer more robust controlled conditions within a trial, and arguably would allow a more exact understanding of the bioactive compounds being delivered by the coffee. Recent evidence suggests that the factor associated with most variability of bioactive compounds in coffee is the preparation type, followed by the degree

of roasting, the type of bean (Arabica versus Robusta), and finally whether it is decaffeinated or not[295]. This highlights that taking account of the preparation type in a study is very important, because of the differences in compounds delivered, as already described. However, the roast and type of bean is rarely taken into account, and would be extremely difficult to ascertain from dietary assessment tools. The caffeination status of coffee, whilst clearly affecting caffeine content, does not affect the variability of bioactive compounds as much as preparation type, roast, and bean. This adds weight to our inclusion of decaffeinated coffee in developing the coffee unit measure, where its non-caffeine components are clearly important. It also implies that supplying coffee within an RCT could allow reduced variability across compounds even if allowing for preparation type and cup size.

6.1.8 Decaffeinated coffee

Beneficial associations between decaffeinated coffee and liver health are not so frequently observed compared to caffeinated coffee. This could be due to the lack of caffeine itself, lack of the synergistic effects it has with other compounds, or because decaffeinated coffee drinkers are a much smaller group within studies and such subgroup analysis may be underpowered. Some of the uncertainty around the coffee versus caffeine debate could be addressed by adding an increasing decaffeinated coffee arm in the RCT. Drinking two cups of decaffeinated coffee was viewed as achievable by 78% of patients in our survey. Again, taking control over the nature of the increased coffee, for example by providing ‘doses’, would also have potential to allow standardisation of the non-caffeine compounds in caffeinated and decaffeinated coffee, such that the lack of caffeine becomes the only difference.

6.1.9 Behaviour change

As discussed in chapter 4, changing individual behaviour to drinking more coffee requires a combination of capacity, opportunity, motivation and flexibility, each governed by a number of different factors. Importantly, drinking an increasing quantity of caffeinated coffee was generally seen as achievable, especially when endorsed by a healthcare professional, and especially when it could lead to benefit to liver health. This high level of

perceived achievability was consistent with findings in the survey phase of the study. Changing coffee consumption patterns after advice from healthcare professionals could be seen in our survey of patients with NAFLD, conducted across three NHS sites, in which one site had a much higher proportion of reports of such advice being given, and accompanied by self-reports of coffee having been increased subsequent to the liver diagnosis. This is an impressive degree of self-reported behaviour change and offers substantial hope that should coffee have proven benefit in reducing the risk of progression in NAFLD, and more health professionals gave the advice, then patients would be amenable to change consumption patterns. Importantly, clinical equipoise still exists, as most participants had not been given any advice from healthcare professionals to increase their coffee intake. Methods to increase the achievability of drinking more caffeinated coffee were discussed in chapter 4 by addressing any barriers within the components of capacity, opportunity, motivation and flexibility. As discussed above, among patients with NAFLD there would be two groups who would have potential to benefit from drinking more coffee. Those drinking zero cups a day would need to overcome challenges of introducing a completely new component in their diet, which for many may offer an unpleasant taste experience. Taste was the most commonly cited reason for those non-coffee drinkers who did not agree to the achievability of starting to drink it. However, our survey suggested that approximately half of all non-coffee drinkers thought that drinking two cups of caffeinated coffee a day was achievable. In a future RCT such non-coffee drinking patients may need to have specific help in introducing coffee into their daily routines, and assistance, such as text messages, might be useful in this regard. Whilst 65% of participants of the CUPLID survey felt that no help was necessary, 30% thought that text messages would be useful. For patients already drinking 1-3 cups of coffee a day, drinking more may not be such a significant change in behaviour, and a group who are probably already invested in the pleasure from the taste, and/or stimulant properties. Drinking more coffee may be different to some other lifestyle behaviour changes in that often advice would resort in taking something, often perceived as enjoyable, away, such as cigarettes or alcohol. The positive taste experience may also be in contrast with some other dietary elements where increase is suggested, such as vegetables, which some people do not enjoy. Importantly, evidence presented in this thesis suggests that substitution may be a solution to participants who feel unable to increase their coffee drinking due to symptoms related to total fluid, or excess caffeine, if they are already consuming other caffeinated beverages.

6.1.10 Eligibility for a future RCT – severity and aetiology

In chapter 5 I concluded by discussing the likely proportion of NAFLD patients who might benefit from increasing (or introducing) coffee (0 and 1-3 cups a day drinkers) and those who might wish to participate in a future RCT. One additional key decision that would need to be made in moving forward would be which sub-group of NAFLD patients should be eligible. As discussed above, coffee might not prevent the development of steatosis, but may reduce the risk of progression. However, within the constraints of an RCT where total duration is likely to be limited by practicalities and cost, maximum efficiency may be achieved by only recruiting patients with more advanced disease, such as those with mild to moderate fibrosis. In the CUPLID survey approximately 40% of participants in liver stiffness group 2 (7-13 kPa) and group 3 (>13 kPa), agreed to the achievability of drinking more coffee and expressed a hypothetical interest in taking part. As such, future recruitment into a proposed RCT would appear achievable when recruited from a secondary care population. Another key decision in recruitment would be whether to include patients in the Both Alcohol and Fatty Liver Disease group (BAFLD). Our survey suggested 27% of our NAFLD patients had a AUDIT-C score of ≥5, suggesting that alcohol may have some aetiology in their fatty liver. As mentioned previously, coffee may have some effect in mitigating the harmful effects of alcohol, and inclusion of this group would seem appropriate. Indeed, this BAFLD group had received a secondary care diagnosis of NAFLD, probably due to under reporting of alcohol intake. The anonymity offered by the CUPLID survey may have reduced under reporting but is unlikely to have eliminated it. Indeed, it is likely that a similar proportion of patients recruited for a future coffee treatment study with diagnoses of NAFLD are likely to have mixed aetiology. Alcohol and obesity are known to interact in the development of liver disease and this mixed group may stand to gain the greatest benefit from increasing coffee intake.

6.1.11 Strengths and limitations

Strengths of the approach used in the conduct of this Doctorate of Medicine degree have been detailed in each section. The overall strength of the evidence lies in the identification of key knowledge gaps between the observational literature, and a future RCT. Lack of a succinct and contemporary overview between coffee and multiple health outcomes was identified as a clear gap and the coffee umbrella review offered a systematic method to make some sense of the vast volume of existing studies. Next, development of the coffee

unit measure offered a unique contribution to coffee ascertainment methodology, especially important with the identification of misclassification within a general, and NAFLD, coffee drinking population. Finally, the mixed methods study offered a robust, pragmatic, method for addressing the arguably most important knowledge gap of all. It benefited from the mixed qualitative and quantitative approach that gave depth and breadth to fully address the research objectives. Arguably within this enquiry, the most important component relates to views on achievability of increasing coffee intake, both in everyday life, and as part of a future RCT among the NAFLD population of patients in whom we would hope to enrol in a future RCT. The positive acknowledgment of achievability, and hypothetical interest in participation, suggests that NAFLD patients would agree to being part of such a study, and those randomised to drinking more coffee would be able to achieve it. However, a feasibility RCT to test recruitment and retention, adherence to the intervention, as well as markers of liver pathology, would offer a logical next step.

Limitations in the approach used in the conduct of the research within this thesis have also been detailed in each section. Summary limitations include the coffee unit measure, which was limited by its arbitrary composition from two components of coffee, and from using data that was extracted from a range of different published estimates, some of which were forty years old. However, the approach offers a starting point, which may spark an interest in the methodology. An improved approach could be the fresh analysis of caffeine and chlorogenic acid content in a large sample of a range of home and coffee shop prepared coffee types using a consistent and validated laboratory analysis. Limitations in time and resources meant that producing empirical data on these variables was outside the scope of this research degree. Next, a limited number of non-coffee drinkers were included in the qualitative phase of the mixed methods study, and there may be nuances across the capacity, opportunity, motivation and flexibility of the non-coffee drinker that remain to be fully explored. However, a representative proportion of non-coffee drinkers participated in the CUPLID survey. Furthermore, despite the excellent return rate and large sample size, the survey was only conducted across secondary care NAFLD patients across three NHS sites. A greater number of sites may have helped to increase the generalisability of findings. Indeed, a future RCT would benefit from a multi-site approach, with a key strength of improving generalisability of the approach and any research findings.

6.1.12 Recommendations and next steps

The main recommendation, informed by work within this thesis, would be to move towards a multi-centre randomised controlled trial in which coffee is tested as a treatment in NAFLD. A further interim step could be to conduct a feasibility randomised controlled trial, with an integrated mechanistic study, in order to address the question of whether the study can be done. Clear progression criteria to a main study should also be included in the design.

The feasibility study would allow:

- Testing the process and acceptability of randomisation
- Testing the process of recruitment in an NHS secondary care setting (including willingness of clinicians to recruit)
- Testing acceptability of the intervention
- Testing adherence to the intervention (completion rates)
- Measurement of key outcomes including estimates, variances, and 95% confidence intervals for the difference between the control and intervention groups, and quantification of missing data

An integrated mechanistic study would inform proof of concept by allowing:

- An exploration of the mechanisms of action of coffee in NAFLD progression
- An exploration of causes of differing responses

However, there are a number of key decisions that would need to be finalised, some of which have been evidenced by the content of the thesis, and include:

- Choosing the exact nature of the intervention between:
    - Increasing coffee by targeting a daily cup or coffee unit intake using patient's preferred coffee preparation type and their own coffee (+/- providing a fixed allowance towards it)
    - Increasing coffee by targeting a daily cup or coffee unit intake by providing pre-measured doses of instant coffee granules
- Deciding whether additional assistance to adhere to the intervention should be provided
- Deciding whether to include a decaffeinated arm in the trial

- Deciding between a parallel or cross-over design
- Deciding on an appropriate time frame for the study in which any effect of coffee on NAFLD progression would be detectable
- Deciding on appropriate non-invasive markers of liver health or mechanistic markers that would allow detection of changes in NAFLD progression within the time frame (such as ALT, ELF, HOMA IR, Lipids)
- Deciding on appropriate markers of coffee/caffeine intake that would be sensitive enough to differentiate between different levels of coffee intake (such as caffeine or Trigonelline)
- Deciding on appropriate progression criteria for advancing to a definitive multi-centre RCT
- Deciding on appropriate methods of monitoring undesirable physical or psychological effects from the intervention

Such decisions need to be made in consultation with a wider research team, including public health academics, clinical and academic hepatologists, clinical scientists, statisticians, health economists, and patient representatives. Such a team would also be necessary to support the application for a research grant for a feasibility/mechanistic study and for a subsequent full RCT.

6.1.13 Conclusion

The body of work in thesis supports a future RCT in which coffee is investigated as a treatment for NAFLD. NAFLD remains an important and highly prevalent clinical and public health issue with predictions that the prevalence will escalate in parallel with the rise in obesity and T2DM. In the absence of any effective pharmaceutical intervention to prevent NAFLD progression, coffee has the potential to offer an affordable and easily accessible alternative should a causal association be confirmed in a definitive RCT. Coffee intake would be better classified in coffee units to overcome the issue of misclassification when using a cup/day measure, and would be unlikely to increase harm outside of pregnancy and for women who are at higher risk of fracture. The thesis has additionally highlighted a range of options for the nature of the coffee intervention, the degree of additional behavioural support required, and encouragingly has suggested that recruitment into an RCT should be possible for a secondary care population of patients with NAFLD.

Appendix A AMSTAR scores for individual studies included in the umbrella review

Table 40: AMSTAR scores for individual studies included in figures 10-14

Outcome	Assessed with	Author	Year	A priori design provided	Duplicate study selection & data extraction	At least two electronic databases searched	Status of publication used as an inclusion criteria	List of included AND excluded studies provided	Characteristics of included studies provided	Scientific quality of included studies assessed	scientific quality of the included studies used appropriately to form conclusions	Appropriate methods to combine studies	Publication bias assessed	Conflict of interest included	Total AMSTAR Score
1st Trimester Preterm Birth	HIGH versus LOW	Maslova	2010	0	0	1	0	0	1	0	0	1	1	1	5
2ndTrimester Preterm Birth	HIGH versus LOW	Maslova	2010	0	0	1	0	0	1	0	0	1	1	1	5
3rdTrimester Preterm Birth	HIGH versus LOW	Maslova	2010	0	0	1	0	0	1	0	0	1	1	1	5
Acute Leukaemia of Child.	HIGH versus LOW	Thomopoulous	2015	0	1	0	0	0	1	1	0	1	1	0	5
All Cancer	1 extra cup/day	Yu	2011	0	1	1	0	0	1	0	0	1	1	1	6
All-cause Mortality	1 extra cup/day	Je	2014	0	0	1	0	0	1	1	0	1	1	1	6
Atrial Fibrillation	1 extra cup/day	Larsson	2015	0	0	1	0	0	1	0	0	1	1	1	5
Birthweight	Coffee versus Control	Jahanfar	2015	1	1	1	1	1	1	1	0	1	0	1	1
Bladder Cancer	1 extra cup/day	Wu	2015	0	1	1	0	0	1	1	1	1	1	1	8
Breast Cancer	1 extra cup/day	Li	2013	0	0	1	0	0	1	0	0	1	1	1	5
Cancer Mortality	1 extra cup/day	Malerba	2013	0	1	1	0	0	1	0	0	1	1	1	6
Cardiovascular Disease	HIGH versus LOW	Ding	2014	0	0	1	0	0	1	1	1	1	1	1	7
Cardiovascular Malf.	HIGH versus LOW	Browne	2006	0	0	1	0	0	1	0	0	1	0	0	3
Cirrhosis	1 extra cup/day	Kennedy	2016	1	1	1	0	0	1	1	1	1	1	1	9
Cognitive Disorder	HIGH versus LOW	Kim	2015	0	1	1	0	0	1	1	1	1	1	1	8
Colon Cancer	HIGH versus LOW	Li	2012	0	0	1	0	0	1	0	0	1	1	1	5
Colorectal Cancer	1 extra cup/day	Galeone	2010	0	1	0	0	0	1	0	0	1	0	1	4
Coronary Heart Disease	HIGH versus LOW	Ding	2014	0	0	1	0	0	1	1	1	1	1	1	7
CVD Mortality	1 extra cup/day	Malerba	2013	0	1	1	0	0	1	0	0	1	1	1	6
Depression	1 extra cup/day	Wang	2016	0	1	1	0	0	1	0	0	1	1	1	6

Diastolic Blood Pressure	Coffee versus Control	Steffen	2012	0	0	1	0	0	1	1	0	1	1	1	6
Endometrial Cancer	1 extra cup/day	Yang	2015	0	0	0	0	0	0	0	0	1	0	1	2
Endometriosis	ANY versus NONE	Chiaffarino	2014	0	0	1	0	0	1	0	0	1	1	0	4
Fracture	1 extra cup/day	Liu	2012	0	0	1	0	0	1	1	0	1	1	1	6
Gallstones	1 extra cup/day	Zhang	2015	0	1	1	0	0	1	1	1	1	1	1	8
Gastric Cancer	1 extra cup/day	Zeng	2015	0	1	1	0	0	1	1	1	1	1	1	8
Glioma	1 extra cup/day	Malerba	2012	0	0	1	0	0	1	0	0	1	1	1	5
GORD	HIGH versus LOW	Kim	2013	0	0	1	0	0	1	1	1	1	1	0	6
Gout	HIGH versus LOW	Park	2016	0	1	1	0	0	1	1	1	1	0	0	6
HDL-Cholesterol	Coffee versus Control	Cai	2012	0	0	1	0	0	1	0	0	1	1	1	5
Heart Failure	HIGH versus LOW	Mostofsky	2012	0	0	1	0	0	1	0	0	1	1	1	5
Hip Fracture	1 extra cup/day	Li	2013	0	0	1	0	0	1	0	0	1	1	1	5
Hypertension	HIGH versus LOW	Zhang	2011	0	0	1	0	0	1	0	0	1	1	1	5
Laryngeal Cancer	HIGH versus LOW	Ouyang	2014	0	1	1	0	0	1	0	0	1	1	1	6
LDL-Cholesterol	Coffee versus Control	Cai	2012	0	0	1	0	0	1	0	0	1	1	1	5
Leukaemia	HIGH versus LOW	Yu	2011	0	1	1	0	0	1	0	0	1	1	1	6
Liver Cancer	1 extra cup/day	Bravi	2013	0	0	0	0	0	1	1	1	1	1	1	6
Liver Fibrosis	ANY versus NONE	Liu	2015	0	0	1	0	0	1	1	1	1	1	1	7
Low Birth Weight	1 extra cup/day	Chen	2014	0	1	1	0	0	1	1	0	1	1	1	7
Lung Cancer	1 extra cup/day	Tang	2010	0	0	1	0	0	1	0	0	1	1	1	5
Melanoma	1 extra cup/day	Wang	2015	0	1	1	0	0	1	1	1	1	1	1	8
Metabolic Syndrome	HIGH versus LOW	Shang	2015	0	1	1	0	0	1	0	0	1	1	1	6
Neural Tube Defects	ANY versus NONE	Li	2015	0	1	1	0	0	1	1	0	1	1	1	7
Non-melanoma skin cancer	HIGH versus LOW	Yu	2011	0	1	1	0	0	1	0	0	1	1	1	6
Oesophageal Cancer	1 extra cup/day	Zheng	2013	0	0	1	0	0	1	0	0	1	1	1	5
Oral Cancer	HIGH versus LOW	Zhang	2015	0	1	1	0	0	1	1	1	1	1	1	8
Oral Cleft Malformations	HIGH versus LOW	Browne	2006	0	0	1	0	0	1	0	0	1	0	0	3

Ovarian Cancer	1 extra cup/day	Braem	2012	0	0	1	0	0	1	0	0	1	1	1	5
Pancreatic Cancer	1 extra cup/day	Ran	2016	0	0	1	0	0	1	0	0	1	1	1	5
Parkinson's Disease	1 extra cup/day	Hernan	2002	0	1	0	0	0	1	0	0	1	1	0	4
Pregnancy Loss	1 extra cup/day	Li	2015	0	1	0	0	0	1	0	0	1	1	1	5
Preterm-birth	Coffee versus Control	Jahanfar	2015	1	1	1	1	1	1	1	0	1	0	1	1
Prostate Cancer	1 extra cup/day	Liu	2015	0	0	1	0	0	1	0	0	1	1	0	4
Rectal Cancer	HIGH versus LOW	Li	2012	0	0	1	0	0	1	0	0	1	1	1	5
Renal Cancer	1 extra cup/day	Huang	2014	0	1	1	0	0	1	0	0	1	0	1	5
Renal Stones	1 extra cup/day	Wang	2014	0	0	1	0	0	1	0	0	1	1	1	5
Rheumatoid Arthritis	HIGH versus LOW	Lee	2015	0	0	1	0	0	1	0	0	1	1	1	5
Small for gestational age	Coffee versus Control	Jahanfar	2015	1	1	1	1	1	1	1	0	1	0	1	1
Stroke	HIGH versus LOW	Ding	2014	0	0	1	0	0	1	1	1	1	1	1	7
Systolic Blood Pressure	Coffee versus Control	Steffen	2012	0	0	1	0	0	1	1	0	1	1	1	6
Thyroid Cancer	ANY versus NONE	Mack	2003	0	0	0	0	0	1	0	0	1	0	1	3
Total Cholesterol	Coffee versus Control	Cai	2012	0	0	1	0	0	1	0	0	1	1	1	5
Triglyceride	Coffee versus Control	Cai	2012	0	0	1	0	0	1	0	0	1	1	1	5
Type II diabetes	1 extra cup/day	Jiang	2014	0	1	1	0	0	1	1	1	1	1	1	8
Urinary Tract Cancer	ANY versus NONE	Zeegers	2001	0	0	1	0	0	1	1	1	1	1	0	6
Venous Thromboembolism	HIGH versus LOW	Lippi	2015	0	0	1	0	0	1	0	0	0	0	1	3

Appendix B GRADE of quality of evidence for coffee consumption and health outcomes

Key

Mortality | Cardiovascular | Cancer | Metabolic | Liver & GI | Pregnancy | Musculoskeletal | Neurological | Gynaecological

Table 41: GRADE Classification of quality of evidence

Mortality Outcome	Assessed with	Author	Year	No. of studies	RCTs	Cohort	Case-control	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication bias	Plausible Confounding	Magnitude of effect	Dose-response gradient	Quality
All-cause Mortality	1 extra cup/day	Je	2014	16	0	16	0	Serious Risk	*Serious Inconsistency	No Serious Indirectness	No Serious Risk	*Undetected	Would reduce effect	No	Yes	⊕⊕◯◯ LOW
Cancer Mortality	1 extra cup/day	Malerba	2013	9	0	9	0	Serious Risk	No serious Inconsistency	No Serious Indirectness	Serious Risk	*Undetected	Would not reduce effect	No	No	⊕◯◯◯ VERY LOW
CVD Mortality	1 extra cup/day	Malerba	2013	16	0	16	0	Serious Risk	Very Serious Inconsistency	No Serious Indirectness	No Serious Risk	*Undetected	Would reduce effect	No	Yes	⊕◯◯◯ VERY LOW

Cardiovascular Outcome	Assessed with	Author	Year	No. of studies	RCTs	Cohort	Case-control	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication bias	Plausible Confounding	Magnitude of effect	Dose-response gradient	Quality
Atrial Fibrillation	1 extra cup/day	Larsson	2015	6	0	6	0	Serious Risk	Serious Inconsistency	No Serious Indirectness	Serious Risk	Undetected	Would not reduce effect	No	No	⊕◯◯◯ VERY LOW
Cardiovascular Disease	HIGH versus LOW	Ding	2014	35	0	34	1	Serious Risk	*Serious Inconsistency	No Serious Indirectness	Serious Risk	Undetected	Would not reduce effect	No	No	⊕◯◯◯ VERY LOW
Coronary Heart Disease	HIGH versus LOW	Ding	2014	22	0	21	1	Serious Risk	Serious Inconsistency	No Serious Indirectness	Serious Risk	Undetected	Would not reduce effect	No	No	⊕◯◯◯ VERY LOW
Diastolic Blood Pressure	Coffee versus Control	Steffen	2012	12	12	0	0	Serious Risk	No Serious Inconsistency	No Serious Indirectness	Serious Risk	**	Would not reduce effect	No	No	⊕⊕◯◯ LOW
HDL-Cholesterol	Coffee versus Control	Cai	2012	9	9	0	0	Serious Risk	No Serious Inconsistency	No Serious Indirectness	Serious Risk	Undetected	Would not reduce effect	No	No	⊕⊕◯◯ LOW
Heart Failure	HIGH versus LOW	Mostofsky	2012	5	0	5	0	Serious Risk	No Serious Inconsistency	No Serious Indirectness	Serious Risk	Undetected	Would not reduce effect	No	No	⊕◯◯◯ VERY LOW
Hypertension	HIGH versus LOW	Zhang	2011	6	0	6	0	Serious Risk	No Serious Inconsistency	No Serious Indirectness	Serious Risk	Undetected	Would not reduce effect	No	No	⊕◯◯◯ VERY LOW
LDL-Cholesterol	Coffee versus Control	Cai	2012	7	7	0	0	Serious Risk	Serious Inconsistency	No Serious Indirectness	No Serious Risk	Undetected	Would not reduce effect	No	No	⊕⊕◯◯ LOW
Stroke	HIGH versus LOW	Ding	2014	17	0	17	0	Serious Risk	Serious Inconsistency	No Serious Indirectness	Serious Risk	Undetected	Would not reduce effect	No	No	⊕◯◯◯ VERY LOW
Systolic Blood Pressure	Coffee versus Control	Steffen	2012	12	12	0	0	Serious Risk	Serious Inconsistency	No Serious Indirectness	Serious Risk	**	Would not reduce effect	No	No	⊕⊕◯◯ LOW
Total Cholesterol	Coffee versus Control	Cai	2012	12	12	0	0	Serious Risk	Serious Inconsistency	No Serious Indirectness	No Serious Risk	Strongly Suspected	Would not reduce effect	No	No	⊕⊕◯◯ LOW
Triglyceride	Coffee versus Control	Cai	2012	6	6	0	0	Serious Risk	Serious Inconsistency	No Serious Indirectness	No Serious Risk	Undetected	Would not reduce effect	No	No	⊕⊕◯◯ LOW
Venous Thromboembolism	HIGH versus LOW	Lippi	2015	3	0	2	1	Serious Risk	Serious Inconsistency	No Serious Indirectness	No Serious Risk	**	Would not reduce effect	No	No	⊕◯◯◯ VERY LOW

Cancer Outcome	Assessed with	Author	Year	No. of studies	RCTs	Cohort	Case-control	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication bias	Plausible Confounding	Magnitude of effect	Dose-response gradient	Quality
All Cancer	1 extra cup/day	Yu	2011	40	0	40	0	Serious Risk	Very Serious Inconsistency	No Serious Indirectness	No Serious Risk	*Undetected	Would reduce effect	No	Yes	⊕◯◯◯ VERY LOW
Bladder Cancer	1 extra cup/day	Wu	2015	6	0	6	0	Serious Risk	No Serious Inconsistency	No Serious Indirectness	Serious Risk	*Undetected	Would not reduce effect	No	No	⊕◯◯◯ VERY LOW
Breast Cancer	1 extra cup/day	Li	2013	15	0	15	0	Serious Risk	No Serious Inconsistency	No Serious Indirectness	No Serious Risk	*Undetected	Would not reduce effect	No	Yes	⊕⊕◯◯ LOW
Colon Cancer	HIGH versus LOW	Li	2012	13	0	13	0	Serious Risk	No Serious Inconsistency	No Serious Indirectness	Serious Risk	Undetected	Would not reduce effect	No	No	⊕◯◯◯ VERY LOW
Colorectal Cancer	1 extra cup/day	Galeone	2010	13	0	0	13	Very Serious Risk	Serious Inconsistency	No Serious Indirectness	No Serious Risk	^^Undetected	Would reduce effect	No	Yes	⊕◯◯◯ VERY LOW
Endometrial Cancer	1 extra cup/day	Yang	2015	7	0	7	0	Serious Risk	**Very Serious Inconsistency	No Serious Indirectness	No Serious Risk	**	Would reduce effect	No	Yes	⊕◯◯◯ VERY LOW
Gastric Cancer	1 extra cup/day	Zeng	2015	9	0	9	0	Serious Risk	Serious Inconsistency	No Serious Indirectness	Serious Risk	Undetected	Would not reduce effect	No	No	⊕◯◯◯ VERY LOW
Glioma	1 extra cup/day	Malerba	2012	3	0	3	0	Serious Risk	Serious Inconsistency	No Serious Indirectness	Serious Risk	Undetected	Would not reduce effect	No	No	⊕◯◯◯ VERY LOW
Laryngeal Cancer	HIGH versus LOW	Ouyang	2014	8	0	1	7	Serious Risk	Serious Inconsistency	No Serious Indirectness	Serious Risk	Undetected	Would not reduce effect	No	No	⊕◯◯◯ VERY LOW
Leukaemia	HIGH versus LOW	Yu	2011	2	0	2	0	Serious Risk	No Serious Inconsistency	No Serious Indirectness	No Serious Risk	*Undetected	Would not reduce effect	No	No	⊕◯◯◯ VERY LOW
Liver Cancer	1 extra cup/day	Bravi	2013	5	0	5	0	Serious Risk	Very Serious Inconsistency	No Serious Indirectness	No Serious Risk	*Undetected	Would reduce effect	^^^Large	Yes	⊕⊕◯◯ LOW
Lung Cancer	1 extra cup/day	Tang	2010	9	0	2	7	Serious Risk	No Serious Inconsistency	No Serious Indirectness	No Serious Risk	Undetected	Would not reduce effect	No	Yes	⊕⊕◯◯ LOW
Melanoma	1 extra cup/day	Wang	2015	7	0	6	1	Serious Risk	*Serious Inconsistency	No Serious Indirectness	No Serious Risk	*Undetected	Would not reduce effect	No	Yes	⊕◯◯◯ VERY LOW

Non-melanoma skin cancer	HIGH versus LOW	Yu	2011	2	0	2	0	Serious Risk	Serious Inconsistency	No Serious Indirectness	No Serious Risk	*Undetected	Would not reduce effect	No	No	⊕◯◯◯ VERY LOW
Oesophageal Cancer	1 extra cup/day	Zheng	2013	NP	0	NP	NP	Serious Risk	*No serious Inconsistency	No Serious Indirectness	Serious Risk	*Undetected	Would not reduce effect	No	No	⊕◯◯◯ VERY LOW
Oral Cancer	HIGH versus LOW	Zhang	2015	3	0	3	0	Serious Risk	No Serious Inconsistency	No Serious Indirectness	Serious Risk	Undetected	Would not reduce effect	No	No	⊕◯◯◯ VERY LOW
Ovarian Cancer	1 extra cup/day	Braem	2012	6	0	6	0	Serious Risk	*Serious Inconsistency	No Serious Indirectness	Serious Risk	*Undetected	Would not reduce effect	No	No	⊕◯◯◯ VERY LOW
Pancreatic Cancer	1 extra cup/day	Ran	2016	9	0	9	0	Serious Risk	*No Serious Inconsistency	No Serious Indirectness	Serious Risk	*Undetected	Would not reduce effect	No	No	⊕◯◯◯ VERY LOW
Prostate Cancer	1 extra cup/day	Liu	2015	9	0	9	0	Serious Risk	* No Serious Inconsistency	No Serious Indirectness	No Serious Risk	*Undetected	Would not reduce effect	No	Yes	⊕⊕◯◯ LOW
Rectal Cancer	HIGH versus LOW	Li	2012	13	0	13	0	Serious Risk	No Serious Inconsistency	No Serious Indirectness	Serious Risk	Undetected	Would not reduce effect	No	No	⊕◯◯◯ VERY LOW
Renal Cancer	1 extra cup/day	Huang	2014	4	0	4	0	Serious Risk	*No Serious Inconsistency	No Serious Indirectness	Serious Risk	**	Would not reduce effect	No	No	⊕◯◯◯ VERY LOW
Thyroid Cancer	ANY versus NONE	Mack	2003	9	0	0	9	Very Serious Risk	**Very Serious Inconsistency	No Serious Indirectness	Serious Risk	**	Would not reduce effect	No	No	⊕◯◯◯ VERY LOW
Urinary Tract Cancer	ANY versus NONE	Zeegers	2001	14	0	0	14	Very Serious Risk	^Very Serious Inconsistency	No Serious Indirectness	No Serious Risk	Undetected	Would not reduce effect	No	No	⊕◯◯◯ VERY LOW

Pregnancy Outcome	Assessed with	Author	Year	No. of studies	RCTs	Cohort	Case-control	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication bias	Plausible Confounding	Magnitude of effect	Dose-response gradient	Quality
1st Trimester Preterm Birth	HIGH versus LOW	Maslova	2010	NP	0	NP	NP	Serious Risk	**Very Serious Inconsistency	No Serious Indirectness	No Serious Risk	*Undetected	Would not reduce effect	No	No	⊕○○○ VERY LOW
2ndTrimester Preterm Birth	HIGH versus LOW	Maslova	2010	NP	0	NP	NP	Serious Risk	**Very Serious Inconsistency	No Serious Indirectness	No Serious Risk	*Undetected	Would not reduce effect	No	No	⊕○○○ VERY LOW
3rd Trimester Preterm Birth	HIGH versus LOW	Maslova	2010	NP	0	NP	NP	Serious Risk	**Very Serious Inconsistency	No Serious Indirectness	Serious Risk	*Undetected	Would not reduce effect	No	No	⊕○○○ VERY LOW
Acute Leukaemia of Childhood	HIGH versus LOW	Thomopoulous	2015	6	0	0	6	Very Serious Risk	Serious Inconsistency	No Serious Indirectness	No Serious Risk	**	Would not reduce effect	No	No	⊕○○○ VERY LOW
Birthweight	Coffee versus Control	Jahanfar	2015	1	1	0	0	Serious Risk	N/A	No Serious Indirectness	Serious Risk	N/A	Would not reduce effect	No	No	⊕⊕○○ LOW
Cardiovascular Malformations	HIGH versus LOW	Browne	2006	4	0	1	3	Serious Risk	Serious Inconsistency	No Serious Indirectness	Serious Risk	**	Would not reduce effect	No	No	⊕○○○ VERY LOW
Low Birth Weight	1 extra cup/day	Chen	2014	2	0	1	1	Serious Risk	Very Serious Inconsistency	No Serious Indirectness	No Serious Risk	*Undetected	Would not reduce effect	No	Yes	⊕○○○ VERY LOW
Neural Tube Defects	ANY versus NONE	Li	2015	7	0	1	6	Serious Risk	Serious Inconsistency	No Serious Indirectness	Serious Risk	Undetected	Would not reduce effect	No	No	⊕○○○ VERY LOW
Oral Cleft Malformations	HIGH versus LOW	Browne	2006	3	0	1	2	Serious Risk	No Serious Inconsistency	No Serious Indirectness	Serious Risk	**	Would not reduce effect	No	No	⊕○○○ VERY LOW
Pregnancy Loss	1 extra cup/day	Li	2015	6	0	4	2	Serious Risk	*Serious Inconsistency	No Serious Indirectness	No Serious Risk	*Undetected	Would not reduce effect	No	Yes	⊕○○○ VERY LOW
Preterm-birth	Coffee versus Control	Jahanfar	2015	1	1	0	0	Serious Risk	N/A	No Serious Indirectness	Serious Risk	N/A	Would not reduce effect	No	No	⊕⊕○○ LOW
Small for gestational age	Coffee versus Control	Jahanfar	2015	1	1	0	0	Serious Risk	N/A	No Serious Indirectness	Serious Risk	N/A	Would not reduce effect	No	No	⊕⊕○○ LOW

Metabolic & Gastrointestinal Outcome	Assessed with	Author	Year	No. of studies	RCTs	Cohort	Case-control	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication bias	Plausible Confounding	Magnitude of effect	Dose-response gradient	Quality
Cirrhosis	1 extra cup/day	Kennedy	2016	7	0	7	0	Serious Risk	Serious Inconsistency	No Serious Indirectness	No Serious Risk	*Undetected	Would reduce effect	No	Yes	⊕⊕◯◯ LOW
Gallstones	1 extra cup/day	Zhang	2015	3	0	3	0	Serious Risk	Serious Inconsistency	No Serious Indirectness	No Serious Risk	*Undetected	Would not reduce effect	No	Yes	⊕◯◯◯ VERY LOW
Gastrointestinal Reflux Disease	HIGH versus LOW	Kim	2013	15	0	0	15	Very Serious Rsik	Serious Inconsistency	No Serious Indirectness	Serious Risk	Undetected	Would not reduce effect	No	No	⊕◯◯◯ VERY LOW
Gout	HIGH versus LOW	Park	2016	2	0	2	0	Serious Risk	No Serious Inconsistency	No Serious Indirectness	No Serious Risk	**	Would not reduce effect	No	No	⊕◯◯◯ VERY LOW
Liver Fibrosis	ANY versus NONE	Liu	2015	8	0	7	1	Serious Risk	Serious Inconsistency	No Serious Indirectness	No Serious Risk	**	Would reduce effect	No	No	⊕◯◯◯ VERY LOW
Metabolic Syndrome	HIGH versus LOW	Shang	2015	4	0	4	0	Serious Risk	No Serious Inconsistency	No Serious Indirectness	No Serious Risk	*Strongly Detected	Would not reduce effect	No	No	⊕◯◯◯ VERY LOW
Renal Stones	1 extra cup/day	Wang	2014	5	0	3	2	Serious Risk	No Serious Inconsistency	No Serious Indirectness	No Serious Risk	Undetected	Would not reduce effect	No	Yes	⊕⊕◯◯ LOW
Type II diabetes	1 extra cup/day	Jiang	2014	20	0	20	0	Serious Risk	*No Serious Inconsistency	No Serious Indirectness	No Serious Risk	*Undetected	Would not reduce effect	No	Yes	⊕⊕◯◯ LOW

Musculoskeletal Outcome	Assessed with	Author	Year	No. of studies	RCTs	Cohort	Case-control	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication bias	Plausible Confounding	Magnitude of effect	Dose-response gradient	Quality
Fracture	1 extra cup/day	Liu	2012	10	0	10	0	Serious Risk	Serious Inconsistency	No Serious Indirectness	Serious Risk	*Strongly Suspected	Would not reduce effect	No	No	⊕◯◯◯ VERY LOW
Hip Fracture	1 extra cup/day	Li	2013	4	0	4	0	Serious Risk	*Serious Inconsistency	No Serious Indirectness	Serious Risk	*Undetected	Would not reduce effect	No	No	⊕◯◯◯ VERY LOW
Rheumatoid Arthritis	HIGH versus LOW	Lee	2015	3	0	3	0	Serious Risk	No Serious Inconsistency	No Serious Indirectness	Serious Risk	*Undetected	Would not reduce effect	No	No	⊕◯◯◯ VERY LOW

Neurological Outcome	Assessed with	Author	Year	No. of studies	RCTs	Cohort	Case-control	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication bias	Plausible Confounding	Magnitude of effect	Dose-response gradient	Quality
Cognitive Dysfunction	HIGH versus LOW	Kim	2015	5	0	5	0	Serious Risk	Serious Inconsistency	No Serious Indirectness	Serious Risk	Undetected	Would not reduce effect	No	No	⊕◯◯◯ VERY LOW
Depression	1 extra cup/day	Wang	2016	5	0	*2	1	Very Serious Risk	Serious Inconsistency	No Serious Indirectness	No Serious Risk	Strongly Suspected	Would not reduce effect	No	Yes	⊕◯◯◯ VERY LOW
Parkinson's Disease	1 extra cup/day	Hernan	2002	4	0	4	0	Serious Risk	**Very Serious Inconsistency	No Serious Indirectness	No Serious Risk	^^Undetected	Would not reduce effect	No	Yes	⊕◯◯◯ VERY LOW

Gynaecological Outcome	Assessed with	Author	Year	No. of studies	RCTs	Cohort	Case-control	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication bias	Plausible Confounding	Magnitude of effect	Dose-response gradient	Quality
Endometriosis	ANY versus NONE	Chiaffarino	2014	3	0	1	2	Serious Risk	Serious Inconsistency	No Serious Indirectness	Serious Risk	Undetected	Would not reduce effect	No	No	⊕◯◯◯ VERY LOW

*based on heterogeneity of overall study
**no heterogeneity published
^based on alternative measure of heterogeneity
^^stated as undetected
^^^based on HIGH versus LOW comparison

Appendix C Semi-structured Interview Topic Guide:

Investigating coffee drinking in people with liver disease

This guide sets out the key questions that w[UNIVERSITY OF Southampton]n interview with approximately 20-32 patients with non-alcoholic fatty liver disease. It gives an outline of the topics to be covered, with suggested questions. It will be proceeded by the participant filling out a brief demographic questionnaire.

Introduction

- Ensure understanding of information sheet and completion of consent form.
  - The interview will be audio recorded.
  - This will then be written out word-for-word (transcribed) and anonymised before analysis takes place.
- Would you like to receive a summary copy of the overall findings?
- We are interested in your experiences and views. There are no wrong answers so please feel able to speak your mind freely.
- Any further questions?
- Participant permission to begin recording

1. General Demographic Details

Captured by accompanying questionnaire

2. Health

How would you describe your health?

(What about your liver? Nature of the liver condition, duration, severity, how well do you feel?)

3. Coffee Consumption Patterns

Please could you now tell me about your coffee drinking?

(If doesn't drink coffee, explore reasons for not drinking coffee, then move to Q 5)

Respond to interviewee but ensure gather following information:

[Nb: Will have some pictures of preparation methods, disposable cups, mugs, glasses to help gather this information]

Reasons for consumption (Enjoyment/Social/Habit/Energy/Alertness)
Patterns or very random?
24-hour recall of consumption – was this a normal day?
Typical pattern of consumption over a week.
What sort of coffee preparation method? (Instant/Filter/Espresso-based/Cafetiere/Aeropress/Siphon)
What sort of coffee? (Brand/Roast/Caffeinated/Decaffeinated)
Location (home/friends/coffee shop/other)
Coffee shop (Independent or national brand)
What sort of cup/mug used? (Glass/cup/mug)
What size of cup/mug used?
How often?
Things added to coffee:

- Milk(Full-fat/Semi/Skimmed)/Cream/Whitener/Soy/Other
- Sugar/Sweetener

Things consumed with coffee:

- Biscuits/Sweets/Cakes/Pastries/Sandwiches

Holds any coffee shop loyalty cards? Use of Promotions in stores?
Stability of consumption pattern over time

4. Effect of liver disease/health on coffee consumption

What effect if any has having liver disease/health problems had on your coffee drinking? What advice have you ever been given from a healthcare professional about your coffee drinking habits?

(eg. change of type, frequency, volume, change of location)

5. Other beverage consumption patterns

Please could you tell me about any other drinks you have which may contain caffeine?

Respond to interviewee but ensure gather following information:

Tea drinking
Cola drinks
Energy drinks

6. Additional sources of caffeine

What other foods do you eat with coffee in them?
What other medicines/sweets/drinks do you consume that may contain caffeine?

7. Perceptions and Barriers to increasing consumption

What are your thoughts about whether drinking coffee is healthy or not?

If drinking coffee was neither good or bad for your health but YOU decided that you wanted to drink two extra cups per day – do you think you would be able to do that?

If yes, explore what this might look like – more of usual coffee drinking described previously or something different?

If no, explore reasons with interviewee and then ask:

If there were HEALTH BENEFITS to increasing your coffee consumption and your doctor asked you to increase your coffee drinking by an extra two cups per day do you think you would be able to do that?

If no, explore reasons in depth with interviewee

If yes, explore what this might look like – more of usual coffee drinking described previously or something different?

Unless interviewee feels that they would NOT be able to increase consumption ask:

What might be some of the difficulties you might have with increasing consumption?

Would there be any other help that you might need to regularly drink an extra two cups each day?

8. Involvement in research

Now I would like to ask you a few theoretical questions about being involved in a different research study to see if coffee consumption changed the natural course of liver disease. One way to do this would be to gather all the people in the study and randomly choose half to increase their coffee consumption, let's say by two extra cups per day, and the other half to carry on with their usual coffee drinking.

What are your thoughts about whether it would be acceptable to be asked to drink two extra cups of coffee each day as part of a research study?

What would the extra two cups look like?

Let the interviewee have freedom to answer but if needs prompts about possible methods then consider:

- Two extra cups of own coffee
- Funded by research project (vouchers towards coffee purchase supermarket/vouchers for high street coffee shop)
- Provided by research project (instant coffee sachets(doses)/jar of instant coffee)

In the context of a research study, would you think that you would need additional help to achieve the extra two cups each day?

Let the interviewee have freedom to answer but if needs prompts about possible methods then consider:

- Electronic reminders (text message/email/App)
- Coffee diary
- Support from a nurse

What are your thoughts about whether it would be acceptable to be randomly allocated to drink your usual amount of coffee as a control measure in a study?

To know whether drinking more coffee could help people with liver disease the study would also need to take blood tests and perform a liver ultrasound scan before and during the study to measure the health of the liver. What are your thoughts about whether these tests would be acceptable?

9. Wrap up & Thank you

Before we wrap up, is there anything else that you would like to say about anything that we have talked about today?

Thank interviewee for participation.

Appendix D Semi-structured

Interview CONSENT FORM

Study Title: Investigating coffee drinking in people with liver disease

Date:	Participant No.

I consent to be interviewed by Dr Robin Poole by initialling the boxes below

I confirm that I have read / had read to me the participant information leaflet dated __/__/__, version __, about this research project and I understand the content. ☐

I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

I understand that my participation is voluntary and that I am free to withdraw at any time, or decline from answering questions, without giving a reason. ☐

I understand that the interview will be audio recorded and written out word-for-word later. The recording will be securely stored in accordance with the Data Protection Act. ☐

I understand that anything I say will be treated confidentially and anonymised before being used only for research purposes. ☐

I agree that direct quotes from my interview may be used and published but these will be anonymised so I will not be identified. ☐

I agree to take part in the research study named above. ☐

Name of participant	Date	Signature
Name of researcher	Date	Signature

For further information please contact Dr Robin Poole, Primary Care and Population Science Academic Unit, University Hospital Southampton, Tremona Road, Southampton, SO16 6YD r.poole@soton.ac.uk 02381 206530

UNIVERSITY OF Southampton

Appendix E Participant Information Sheet about the qualitative research

(Semi-structured Interviews)

Study Title: Investigating coffee drinking in people with liver disease (IRAS reference number: 223905)

We would like to invite you to take part in our research study. Before you decide we would like you to understand why the research is being done and what it would involve for you. One of the researchers will go through this information sheet with you and answer any questions you have. This initial discussion should take about 10 minutes and you can talk to others about the study if you wish.

Please ask us if there is anything that is not clear.

What is the purpose of the study?

Coffee is enjoyed as a drink by millions of people all over the world and lots of research has been done to find out whether it is good or bad for our health. To date, the overall body of research suggests that drinking coffee does not seem to be harmful. In fact, there is some evidence to suggest that drinking coffee is linked to a lower risk of certain conditions such as liver disease.

However, the current evidence for this is what researchers describe as 'low quality' due to the types of studies used and we cannot rely on this to tell us whether people with liver disease might experience benefit from drinking more coffee or not. More research is needed to help us find this out. The first part of this research (the present study) is designed to find out more about the patterns of coffee drinking that exist in people with liver disease, views about drinking more coffee and opinions on proposed future research.

We would like to achieve this by conducting some interviews. These take the form of one-on-one conversations and last approximately 45 minutes. We are inviting approximately 30 adults, over the age of 18, to be involved with this part of our research. The research only involves a conversation and nothing else will be expected of you.

Why have I been invited?

You will have been invited to take part in the research if you have one of the specific types of liver conditions in which we are particularly interested.

We would like to get a wide range of views so we are asking a variety of different people with liver disease to take part.

Do I have to take part?

It is up to you whether to take part in this study. We will describe what will happen and go through this information sheet. If you agree to take part, we will then ask you to sign a consent form. You are free to change your mind and not take part at any time and you do not need to give a reason. This will not affect the care you receive in the NHS in anyway.

What will happen to me if I take part?

Taking part will involve one face-to-face, or telephone, interview with a researcher and will take between 30 minutes and one hour.

We will be making an audio recording of the interview and then afterwards we will write everything out word-for-word. We will use the findings from all the interviews to help us identify the main themes across all the participants. **We would use some direct quotes to explain some of the themes. However, we will never disclose who we interviewed or who said what.**

What will I have to do?

At the interview, we will ask you some questions about yourself, about your general health and liver condition, and about the coffee that you drink. We will also ask your views on what you think about drinking more coffee. Finally, we will ask your opinion about some further research that we may do at a later stage to see if you think it is a good idea or not.

We ask that you give honest answers to the questions.

Expenses and payments

We would hope to conduct the interview at the hospital after another appointment you may have, arrange for you to come back on another occasion. Occasionally we may be able to do the interview on the telephone or in another location. **Once the interview is finished, you will receive a complementary car park exit ticket and £10 shopping voucher to thank you for taking part.**

What are the possible benefits of taking part?

Your involvement will help our team of researchers understand more about current coffee drinking patterns in people with a liver condition and help us to plan further research to find out whether drinking more coffee is beneficial to liver health.

Will my taking part in the study be kept confidential?

We will keep your participation in the study confidential. We will not share any of the answers you give to the questions with anybody else. When the recordings are written out word-for-word we will not include any information that could identify you. The only people who will see the anonymised individual results will be our research team from the University of Southampton. Summaries of the results may be shared with our research colleagues at the University of Edinburgh but the identity of who said what will never be shared. Anonymised quotes may be used in reports or publications.

The information will be collected by the researchers and stored on a secure computer server at the University of Southampton. Only our research team will have access to this.

Information that can identify a person (name, age, date of birth, address etc) will be removed and kept separately in paper form. Each person who takes part will be given a number that will replace the identifiable information so only the research team will be able to match the information with a specific person.

Any paper records and audio recordings will be kept securely locked at the University of Southampton and only the researchers will have access. **The paper forms will be kept for approximately 12 months until the study period is complete. The audio recordings will be destroyed once they been written out word-for-word and the resulting anonymised documents will be kept for a minimum of fifteen years in line with University of Southampton, Faculty of Medicine, policy on storage of research data.**

All information (data) will be kept in line with the Data Protection Act 1998.

Are there any circumstances in which confidentiality is broken?

We will treat all the answers given to the specific questions in the interview in confidence. However, there are rare situations in which a participant gives additional information that researchers are required by law to share. Information will be disclosed and confidentiality breached ONLY in the following circumstances:

- When information given by you concerns the abuse, harm or neglect of a child or when we have reason to believe that a child is being abuse, harmed or neglected.
- If by keeping information confidential you or another person is likely to suffer serious injury
- If the Police have a court order for specific information relating to you
- We are obliged to pass information to the relevant authorities if the information relates to the Prevention of Terrorism Act (1990).
- If you disclose information relating to an offence either committed or planned.
- If you disclose information relating to a substantial breach of professional standards by a third party

If any of these circumstances apply every effort will be made to inform you of a disclosure and to encourage you to take the appropriate steps yourself **but this information would be passed on to the relevant authorities.**

What will happen if I don't want to carry on with the study?

You are free to withdraw from the study at any time, decline from answering certain questions, and you do not need to provide your reasons for doing so. This will not affect the care you receive in the NHS.

Who is organising and funding the research?

The University of Southampton is leading and funding the research. The Chief Investigator is Dr. Robin Poole and this study will form part of a programme of work that will lead to further research in coffee consumption and liver disease. It will also contribute towards a post-graduate degree being conducted by Dr Robin Poole.

What if there is a problem?

If you have a problem about any part of this study, you should speak to one of the researchers who will do their best to answer your questions or speak to Dr Robin Poole via **02381 206530.** If you remain unhappy and wish to complain formally, you can do this by contacting:

Research Governance & Integrity Team
University of Southampton
Highfield,
Southampton
SO17 1BJ
Phone 023 8059 5058
researchintegrity@soton.ac.uk

What will happen to the results of the research study?

We will provide a summary of the findings to any person who takes part in the study if they would like to receive this. We hope to publish the results and share this with the wider research community. We will not identify any individual participants in any report or publication.

Who has reviewed the study?

All research is looked at by independent groups of people, called Research Ethics Committees, to ensure your interests are protected. The present study has been reviewed and given favourable opinion by the NHS Health Research Authority. The research has also been designed in collaboration with a dedicated Public and Patient Involvement team.

For further information please contact Dr Robin Poole, Primary Care and Population Science Academic Unit, University Hospital Southampton, Tremona Road, Southampton, SO16 6YD r.poole@soton.ac.uk 02381 206530

UNIVERSITY OF Southampton

Appendix F Pre-interview demographic questionnaire

Study Title: Investigating coffee drinking in people with liver disease

Thank you for completing this pre-interview questionnaire. The questionnaire remains anonymous but helps us with our research to ensure that we interview a wide range of people.

1. Do you currently drink any coffee?	**Yes**	☐
	No	☐

2. What is you gender?	**Male**	☐
	Female	☐
	Other	☐

3. What is your age group?	**18-24**	☐
	25-34	☐
	35-44	☐
	45-54	☐
	55-64	☐
	65-74	☐
	75-84	☐
	85+	☐

4. What is your ethnicity? (Please tick)	**White**	**British**	
		Irish	
		Other	
	Mixed	**White & Asian**	
		White & Black African	
		White & Black Caribbean	
		Any other mixed background	
	Chinese		
	Asian or Asian British	**Bangladeshi**	
		Indian	
		Pakistani	
		Any other Asian background	
	Black or Black British	**African**	
		Caribbean	
		Any other black background	
	Other ethnicity		

5. What is your employment status?	**Paid employment or self-employed**	☐
	Retired	☐
	Looking after home and/or family	☐
	Unable to work because of sickness or disability	☐
	Unemployed	☐
	Doing unpaid or voluntary work	☐
	Full or part-time student	☐
	None of the above	☐
	Prefer not to answer	☐

6. What qualifications do you have?	**College or university degree**	☐
	A-levels/AS levels or equivalent	☐
	O-levels/GCSEs or equivalent	☐
	CSEs or equivalent	☐
	NVQ or HND or HNC or equivalent	☐
	Other professional eg. Nursing, teaching	☐
	None of the above	☐
	Prefer not to answer	☐

7. Do you own or rent your accommodation?	**Own outright (you or someone in your household)**	☐
	Own with a mortgage	☐
	Rent from local authority, local council, or housing association	☐
	Rent from private landlord or letting agency	☐
	Pay part rent and part mortgage (shared ownership)	☐
	Live in accommodation rent free	☐
	None of the above	☐
	Prefer not to answer	☐

8. Including yourself, how many people are living together in your household? **(If you live alone, enter '1')**	

9. How are other people who live with you related to you? **(You can select more than one answer)**	**Husband, wife or partner**	☐
	Son and/or daughter (including step-children)	☐
	Brother and/or sister	☐
	Mother and/or father	☐
	Grandparent	☐
	Grandchild	☐
	Other related	☐
	Other unrelated	☐
	Prefer not to answer	☐

10. What is your height (to the nearest unit measurement) in feet and inches, or metres?		**FEET**		**INCHES**
	or			
		M		**Cm**

11. What is your weight (to the nearest unit measurement) in stone or kilograms?		**STONE**
	or	
		Kilograms

12. Have you ever been diagnosed as	**Yes**	☐
	No	☐

having heart disease?		

13. Have you ever been diagnosed as having had a stroke?	**Yes**	☐
	No	☐

14. Have you ever been diagnosed as having type II diabetes?	**Yes**	☐
	No	☐

15. Do you smoke cigarettes?	**Yes**	☐
	No (move to Q 17)	☐

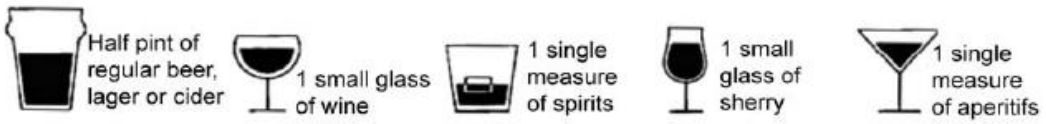
16. How many cigarettes do you smoke each day?	**0-9**	☐
	10-19	☐
	≥20	☐

17. Do you smoke e-cigarettes?	**Yes**	☐
	No (move to Q 18)	☐

18. How many e-cigarettes do you smoke each day?	**0-9**	☐
	10-19	☐
	≥20	☐

Q19 to 21 refer to alcohol. Please use following as a guide

This is one unit of alcohol…



…and each of these is more than one unit

19. How often do you have a drink containing alcohol? (please choose one)	**Never**	☐
	Monthly or less	☐
	2-4 times per month	☐
	2-3 times per week	☐
	4+ times per week	☐

20. How many units of alcohol do you drink on a typical day when you are drinking? Refer to the chart above if needed	**1-2**	☐
	3-4	☐
	5-6	☐
	7-9	☐
	10+	☐

21. How often have you had 6 or more units if female, or 8 or more if male, on a single occasion in the last year?	**Never**	☐
	Less than monthly	☐
	Monthly	☐
	Weekly	☐
	Daily or almost daily	☐

Thank you for completing this questionnaire

Appendix G Qualitative study recruitment poster

LOVE COFFEE?
HATE COFFEE?
WE NEED YOU

Would you like to help us with research to **understand more about coffee drinking in people with certain liver conditions**? Whether you love coffee or hate coffee, we need you! **Taking part involves a face-to-face or telephone interview with a researcher on a single occasion and will last up to one hour**. You will be asked questions about your coffee drinking and views about other research we are planning.

As a thank you for taking part you will be given a **FREE car park exit ticket and a £10 shopping voucher**.

If you are interested in taking part then please discuss this with your doctor during your appointment. We are currently investigating only certain types of liver condition and your doctor will be able to advise whether you are suitable or not.

The research is being conducted by researchers from the University of Southampton, in conjunction with liver doctors from University Hospital Southampton. It has received full NHS ethical committee approval. (Approval no:_____)

Appendix H CUPLID Survey Procedure

This document is to clarify the procedure for conducting the coffee consumption postal survey of 270 randomly selected patients with NAFLD from an existing database, stratified into three groups based on liver stiffness (<7 KPa, 7-13 KPa, and >13 KPa). The procedure includes the first phase send out followed by a reminder phase after three weeks. The two phases combined will last six weeks.

Documents supplied are shown in table 1:

Table 42: Supplied documents

Document Name	Type
1_UHS_Localised_Cover_letter_version_v1.6_25_09_2018_MM	Word document
2_UHS_localised_Survey_participant_information_sheet_v1.0_25_09_2018	Word document
3_UHS_localised_Coffee_Consumption_Questionnaire_v1.8_07_08_2018	Word document
4_UHS_Localised_Reminder_letter_v1.6_25_09_2018_MM	Word document
A_UHS_CUPLID_codes_v1.0_07_11_2018	Excel sheet
B_UHS_Localised_CUPLID_Code_Labels	Word document
C_CUPLID_return_envelope_address_labels	Word document
D_CUPLID_outward_envelope_address_labels_MM	Word document

A number of items should be printed and prepared ahead of the participant identification procedure as shown in table 2.

Table 43: Documents to print/prepare prior to participant identification process

1. Print 270 Participant information sheets (doc 2) Notes: *i. 1 double-sided sheet of A4 per information sheet*	☐
2. Print 270 Coffee consumption survies (doc 3) Notes: *i. 10 double-sided sheets of A4 per questionnaire*	☐
3. Print CUPLID unique coded sticky labels (doc B) Notes: *i. Set up for Avery No. L7654 (45.7 x 25.4 x 40) = 7 sheets of A4*	☐
4. Print CUPLID Freepost return envelope sticky labels (doc C) Notes: *i. Set up for Avery No. L7165 (67.7 x 99.0 x 8) = 34 sheets of A4*	☐
5. Order 270 stamps unless franking machines are to be used Notes: *i. Only needed for outgoing envelopes*	☐
5. Order 540 C4 size (22.9 x 32.4 cm) white envelopes (no address window), self-sealing tear off strip Notes: *i. Each participant send out requires two envelopes*	☐
6. Stick one CUPLID freepost return address label onto the centre of each of 270 C4 envelopes and fold each in half ready for insertion into each outgoing envelope pack	☐

The prepared materials in table 2 will be used once the participants are identified and added to the CUPLID coded Excel sheet. The process for participant identification and questionnaire posting is detailed in table 3.

Table 44: Phase one participant identification and questionnaire posting procedure

1. Access local NAFLD Database (member of clinical team)	☐
2. Split NAFLD patients into three groups stratified by liver stiffness (<7, 7-13, >13 kPa)	☐
3. Use random number generator (eg. https://www.random.org) to select random entry in database from first liver stiffness group (<7 KPa)	☐
4. Add patient **NHS number (or hospital ID), Gender, Age, Title, Name and Address** to first empty row of CUPLID coded Excel sheet (doc A). Notes: i. *Ensure Title, Forename, Surname, and each line of address added as separate columns to ensure mail merge will work properly* ii. *If NAFLD database does not include patient address, cross reference to NHS database to extract information*	☐
5. Repeat steps 3 and 4 until 90 patients have been added to CUPLID coded Excel sheet from liver stiffness group 1 (<7 KPa). Save the file as you go along. Notes: *i. Ensure no duplicate entries by keeping a separate note of which random numbers have been used. If a number is repeated, generate a further number until a unique number is produced*	☐
6. Repeat steps 3 to 5 for liver stiffness group 2 (until a further 90 patients added), and then repeat again for liver stiffness group 3 (until a further 90 patients added) Notes: *i. The CUPLID coded Excel sheet contains three different columns of CUPLID IDs – one for each liver stiffness group (rows 2-91 for <7 KPa, rows 92-181 for 7-13 KPa, and rows 182-271 for >13 KPa)* ii. *There should now be 270 rows of data in the completed CUPLID coded Excel sheet* iii. *Ensure you save again before moving to the next step*	☐
7. Open cover letter word document (doc 1). If prompted on opening the document link to the CUPLID coded Excel sheet you have just completed. Alternatively if the document opens without prompt click on 'mailings' tab in the top menu and click on 'select recipients' button and choose 'use existing list' from the dropdown menu. Link to your saved CUPLID coded Excel sheet.	☐
8. Click on 'preview results' button and ensure that mail merge fields are correctly displayed. There should be 270 records.	☐
9. If looks correct, click on 'finish & merge' button and 'print documents'. You can print cover letters all in one go or select a range. Notes: *i. Ensure printed cover letters are kept in sequential order*	☐
10. Hepatology consultant signs each printed cover letter	☐
11. Identify first signed cover letter	☐
12. Take a printed questionnaire and add CUPLID ID sticker to the front that corresponds with the patient on the first cover letter by cross referencing with the CUPLID coded Excel sheet	☐
13. Hand-write the patient name and address onto the front of a C4 envelope Notes: *i. The successful pilot survey used hand-written outgoing envelopes that evidence suggests improves return rates in postal surveys. However, a mail merge address grid (doc D) has been included if the local site does not have time to hand write each envelope and can be used instead.*	☐

14. Place the cover letter, coded questionnaire, participant information sheet, and folded stickered return envelope into the envelope from step 13 and seal the envelope closed	☐
15. Repeat steps 11 to 14 for all 270 participants	☐
16. Add stamps or frank each envelope in turn, and post	☐

***** Phase one is now complete *****

Phase two involves sending out reminder letters. Approximately three weeks following phase one the research team will supply a second Excel sheet (doc E) with the 'return_status' column filled in where 'NR' represents 'Non-return' of CUPLID codes from each liver stiffness group. A further document containing the questionnaire labels for the non-returners will also be supplied (doc F). The procedure for generating the reminder letters is detailed in table 4.

Table 45: Reminder letter generation and questionnaire posting procedure

1. Prepare the corresponding number of printed participant information sheets (doc 2), questionnaires (doc 3), CUPLID ID stickers (new doc F) and return address labels depending on numbers needed	☐
2. Open your CUPLID coded database	☐
3. Open the 'doc E' Excel sheet that will have been supplied by the research team	☐
4. Copy entire 'return_status' column from 'doc E' sheet and paste into the 'return_status' column of the CUPLID coded database previously constructed by clinical team. Notes *i. Make a visual check to ensure added return_status column matches codes in previously constructed CUPLID coded Excel sheet before proceeding*	☐
5. Save the revised CUPLID coded Excel sheet	☐
6. Open reminder letter word document (doc 4). If prompted on opening the document link to the CUPLID coded database constructed for the initial send out. Alternatively if the document opens without prompt click on 'mailings' tab in the top menu and click on 'select recipients' button and choose 'use existing list' from the dropdown menu. Link to your original saved CUPLID coded Excel sheet (now with the new column inserted).	☐
7. Click on 'preview results' button and ensure that mail merge fields are correctly displayed. There will still be 270 records showing but only those with 'NR' in the 'return_status' column will be merged when printed in step 8.	☐
8. If looks correct, click on 'finish & merge' button and 'print documents'. You can print reminder letters all in one go or select a range. Notes: i. *Ensure printed reminder letters are kept in sequential order*	☐
9. Hepatology consultant signs each printed reminder letter	☐
10. Identify first signed reminder letter	☐
11. Take a printed questionnaire and add CUPLID ID sticker to the front that corresponds with the patient on the first reminder letter by cross referencing with the CUPLID code Excel sheet	☐
12. Hand-write the patient name and address onto the front of a C4 envelope	☐

Notes: *The successful pilot survey used hand-written outgoing envelopes that evidence suggests improves return rates in postal surveys. However, a mail merge address grid (doc D) has been included if the local site does not have time to hand write each envelope and can be used instead. If the site has used the mail merge address grid in phase one, the research team will supply a new grid that will only print the labels for the non-returns (NR).*	
13. Place the reminder letter, coded questionnaire, participant information sheet, and folded stickered return envelope into the envelope from step 11 and seal the envelope closed	☐
14. Repeat steps 9 to 12 for all NR participants	☐
15. Add stamps or frank each envelope in turn and post	☐

After a further three week period from phase two send out, the research team will supply a final Excel sheet of with a new 'return_status' labelled as '2NR' or 'Second Non-returns'. This should be copied and pasted to replace the 'return_status' column used in the second phase. The aggregated ages and genders of the 2NRs should be computed and emailed back to the research team using the following characteristics:

Table 46: Characteristics of second non-returners

Characteristic		Number of 2NRs
Gender	Male	
	Female	
Age	18-24	
	25-34	
	35-44	
	45-54	
	55-64	
	65-74	
	75-84	
	85+	

*****End of procedure*****

***** Thank you for all your help in conducting the CUPLID survey *****

Appendix I CUPLID postal survey cover letter

University Hospital Southampton NHS
NHS Foundation Trust

UNIVERSITY OF Southampton

Department of Hepatology
University Hospital Southampton NHS Foundation Trust
Tremona Road
Southampton
SO16 6YD

Date to be inserted

«Title» «Forename» «Surname»
«Address_Line_1»
«Address_Line_2»
«Address_Line_3»
«County»
«Postcode»

Dear «Title» «Surname»

Existing research suggests coffee drinking **might** be good for liver health but we need to do more research before we can be certain. As a first step, we are currently undertaking a survey of people with liver conditions to understand more about their coffee drinking, their views about increasing coffee intake, and their opinions about further research that we may do on coffee in the future. We are collaborating with a research team from the University of Southampton to conduct the research and analyse the results.

Taking part is completely optional, but whether you **like coffee or dislike coffee**, we would really appreciate your time in **completing the enclosed questionnaire**, and posting both back to us in the pre-paid envelope.

The questionnaire should take approximately 15 minutes to complete and your answers will **remain entirely anonymous**. There is however a unique code attached to each questionnaire that will help us monitor which questionnaires have been returned. Thank you. We are very grateful for your participation.

Yours sincerely

Dr Consultant Name
Consultant Hepatologist

The research is a collaboration between University Hospital Southampton and the University of Southampton Primary Care and Population Science Academic Unit and has full NHS ethical approval (no: 17/WS/0231). The research team will **not** have access to any of your personal information. **If you would like to understand more about the research then please read the accompanying participant information sheet**. If you would like to know how personal

information is used by the NHS for purposes of health research then please visit:
https://www.hra.nhs.uk/information-about-patients/

Appendix J CUPLID postal survey participant information sheet

Participation Information Sheet; Lead researcher: Dr Robin Poole; ERGO No. 30378.

You are being invited to take part in the above research study. To help you decide whether you would like to take part or not, it is important that you understand why the research is being done and what it will involve. Please read the information below carefully before you decide to take part in this research.

1. What is the research about and what data will be collected? Existing research suggests that coffee may be beneficial for liver health but we need to do further research before we can be sure. The present survey aims to explore patterns of coffee drinking, views about drinking more coffee, and opinions on our future research. We also ask for other details about you to understand more about the people who have taken part. Even if you do not currently drink coffee we would welcome your participation.

The **University of Southampton** and **University Hospital Southampton NHS Foundation Trust** are collaborating for this research. The University of Southampton is leading and funding the research. The Chief Investigator is Dr Robin Poole and this study will form part of a programme of work that will lead to further research in coffee consumption and liver disease. It will also contribute towards a post-graduate degree being conducted by Dr Robin Poole.

2. Do I have to take part? No, it is entirely up to you. **We accept your consent to take part in this research by return of a completed questionnaire**. **If you do not consent to take part then please take no further action.** You will be sent a reminder about the research after three weeks but will not be contacted again thereafter. **Your usual clinical care will not be affected whether you decide to take part or not.**

3. What will happen to me if I take part? **You will only be asked to complete the enclosed questionnaire and return it in the pre-paid envelope.**

4. Why have I been asked to participate? We have sent a questionnaire to approximately 800 people with certain types of liver condition.

5. Are there any benefits or risks from taking part? Your questionnaire answers will help further the understanding between coffee drinking and liver health. There are no anticipated risks from taking part.

6. Will my participation be kept confidential? Your participation and the information we collect about you during the course of the research will be kept confidential. The questionnaire does not contain any information that will directly identify you (personally identifiable information). At no point will your clinical team have access to the results of your

questionnaire, and at no point will the research team have access to your personal information. Returned questionnaires will be securely stored in the academic research unit at University Hospital Southampton.

7. What happens if I change my mind? Once a questionnaire has been returned it would not be possible for the research team to identify you and therefore not possible to withdraw your questionnaire data from the study.

8. What will happen to the results of the research? The combined results of the survey will be used to write a research report, and may be used in publications, conference abstracts or presentations. No personally identifiable information will ever be included in any research outputs.

9. Where can I get more information? If you have any questions or concerns please contact Dr Robin Poole, Primary Care and Population Sciences Academic Unit, Faculty of Medicine, Mail Point 805, Level C, South Academic Block, University Hospital Southampton, Tremona Road, Southampton, Hampshire, SO16 6YD Telephone: + 44 (0) 23 8120 6742 Email: r.poole@soton.ac.uk

10. What happens if there is a problem? If you have any further concerns about the study, or if you wish to complain formally, you can do this by contacting: Research Governance & Integrity Team University of Southampton, Highfield, Southampton , SO17 1BJ, Phone 023 8059 5058 Email: rgoinfo@soton.ac.uk

Data Protection Privacy Notice: The University of Southampton conducts research to the highest standards of research integrity. As a publicly-funded organisation, the University has to ensure that it is in the public interest when we use personally-identifiable information about people who have agreed to take part in research. This means that when you agree to take part in a research study, we will use information about you in the ways needed, and for the purposes specified, to conduct and complete the research project. Under data protection law, 'Personal data' means any information that relates to and is capable of identifying a living individual. The University's data protection policy governing the use of personal data by the University can be found on its website (https://www.southampton.ac.uk/legalservices/what-we-do/data-protection-and-foi.page).

This Participant Information Sheet tells you what data will be collected for this project and whether this includes any personal data. Please ask the research team if you have any questions or are unclear what data is being collected about you.

Our privacy notice for research participants provides more information on how the University of Southampton collects and uses your personal data when you take part in one of our research projects and can be found at http://www.southampton.ac.uk/assets/sharepoint/intranet/ls/Public/Research%20and%20Integrity%20Privacy%20Notice/Privacy%20Notice%20for%20Research%20Participants.pdf

Any personal data we collect in this study will be used only for the purposes of carrying out our research and will be handled according to the University's policies in line with data protection law. If any personal data is used from which you can be identified directly, it will not be disclosed

to anyone else without your consent unless the University of Southampton is required by law to disclose it.

Data protection law requires us to have a valid legal reason ('lawful basis') to process and use your Personal data. The lawful basis for processing personal information in this research study is for the performance of a task carried out in the public interest. Personal data collected for research will not be used for any other purpose.

For the purposes of data protection law, the University of Southampton is the 'Data Controller' for this study, which means that we are responsible for looking after your information and using it properly. The University of Southampton will keep identifiable information about you for 10 years after the study has finished after which time any link between you and your information will be removed.

To safeguard your rights, we will use the minimum personal data necessary to achieve our research study objectives. Your data protection rights – such as to access, change, or transfer such information - may be limited, however, in order for the research output to be reliable and accurate. The University will not do anything with your personal data that you would not reasonably expect.

If you have any questions about how your personal data is used, or wish to exercise any of your rights, please consult the University's data protection webpage (https://www.southampton.ac.uk/legalservices/what-we-do/data-protection-and-foi.page) where you can make a request using our online form. If you need further assistance, please contact the University's Data Protection Officer (data.protection@soton.ac.uk).

***** Thank you for taking the time to read this information and for your consideration in taking part *****

Appendix K CUPLID postal survey questionnaire

University Hospital Southampton NHS Foundation Trust

University of Southampton

Department of Hepatology, Gastrointestinal and Liver services, University Hospital Southampton NHS Foundation Trust, Tremona Road, SO16 6YD

CUPLID ID:

Coffee drinking and liver health Questionnaire

Takes 10-15 minutes to complete

Coffee drinking and liver health Questionnaire

Thank you very much for taking time to complete this questionnaire. Your answers will help us understand more about coffee drinking in people with liver conditions and plan the next part of our research into liver health.

Instructions:

Please complete the questionnaire by ticking the boxes that represent the best answer to each question. In some places you may need to add some words or numbers to help clarify answers. Some questions may not be relevant to you and you will be directed to skip them.

The survey is divided into seven sections.

In the first four sections we will ask you about the beverages that you drink on a regular basis.

By regular we mean drinking one of these at least once each week.

Section 1 is about coffee (including decaffeinated coffee)
Section 2 is about tea
Section 3 is about cola drinks
Section 4 is about energy drinks

Section 5 is about your views on drinking more coffee
Section 6 is about your opinion on our plan for further research
Section 7 contains a few other questions about you

The questionnaire should only take about 10 to 15 minutes to complete.

Please complete all sections.

The survey begins on the next page

Section 1

COFFEE

1. Do you drink coffee <u>at least once a week, most weeks</u>? (Includes decaffeinated coffee)			
Yes	☐	No (Please now go to Section 2 'Tea' on Page 5)	☐

2. In a <u>typical week</u>, how many <u>days</u> would you drink coffee?	1☐ 2☐ 3☐ 4☐ 5☐ 6☐ 7☐

3 a. On a <u>typical *week* day (or working day),</u> how many <u>cups of coffee</u> would you drink?	1☐ 2☐ 3☐ 4☐ 5☐ 6☐ 7☐ 8☐ 9☐ 10☐more than 10☐
3 b. On a <u>typical *weekend* day (or non-working day),</u> how many <u>cups of coffee</u> would you drink?	1☐ 2☐ 3☐ 4☐ 5☐ 6☐ 7☐ 8☐ 9☐ 10☐more than 10☐

4. How has having a liver condition affected your coffee drinking? Please tick ONE of the answers below	
I drink a lot less coffee now	☐
I drink slightly less coffee now	☐
My coffee drinking has not changed	☐
I drink slightly more coffee now	☐
I drink a lot more coffee now	☐

5. Have you ever been advised to change your coffee drinking by a healthcare professional? (Please tick all that apply)	
No	☐
Yes to drink less coffee	☐
Yes to drink more coffee	☐

6. <u>Please tell us about all the cups of coffee you drank yesterday?</u>
(Please write down the number of cups of each type of coffee you drank and tick the approximate cup sizes. If you did not drink any coffee yesterday then please move onto question 7)

	Number of cups of coffee you drank yesterday	Approximate cup size					
		S 	**S+** 	**M** 	**M+** 	**L** 	**X L** 
		(170mls) (6 oz) Home Cup	(227mls) (8 oz) Home Mug	(284mls) (10oz) Latte glass	(340mls) (12oz) Coffee Shop Medium/ Regular	(454mls) (16oz) Coffee Shop Large	(568mls)(20oz) Coffee Shop Extra Large
Example coffee	2	☐	☑	☐	☐	☐	☐
Instant		☐	☐	☐	☐	☐	☐
Filter		☐	☐	☐	☐	☐	☐
Cafetière		☐	☐	☐	☐	☐	☐
Capsule/pod		☐	☐	☐	☐	☐	☐
Cappuccino		☐	☐	☐	☐	☐	☐
Café Latte		☐	☐	☐	☐	☐	☐
Flat white		☐	☐	☐	☐	☐	☐
Americano		☐	☐	☐	☐	☐	☐
Mocha		☐	☐	☐	☐	☐	☐
Single Espresso		**Espresso cup**					
Double Espresso		**Espresso cup**					
Iced coffee		☐	☐	☐	☐	☐	☐
Other – please state:		☐	☐	☐	☐	☐	☐

7. What type of day was it for you yesterday?	
Week day (or working day) ☐	**Weekend (or non-working day) ☐**

8. What types of coffee do you drink on a regular basis? (At least once a week, most weeks) Please tick all that apply.			
Instant	☐	Flat white	☐
Filter	☐	Americano	☐
Cafetière	☐	Mocha	☐
Capsule/pod	☐	Single espresso	☐
Cappuccino	☐	Double espresso	☐
Café Latte	☐	Iced coffee	☐
Other, please state:			
9. Is the coffee you usually drink caffeinated or decaffeinated?			
Caffeinated	☐	Decaffeinated	☐
10. What type of milk, if any, do you usually add to your coffee?			
None	☐	Semi-skimmed	☐
Skimmed milk	☐	Full-fat	☐
Cream	☐	I'm not sure	☐
11. What type of additional sweetness, if any, do you usually add to your coffee?			
None	☐	Artificial sweetener	☐
Sugar	☐	Flavoured syrup	☐
Other - Please state:			
12. Where do you drink your coffee (Tick all that apply)?			
Home	☐	Coffee shop or cafe	☐
Work	☐	Restaurant	☐
Other - Please state:			

Please now move onto section 2 on the next page

Section 2

TEA(Not including fruit teas)

13. Do you drink tea at least once a week?			
Yes	☐	No (Please now go to section 3 'cola' on page 7)	☐

14. In a typical week how many days would you drink tea?	1☐ 2☐ 3☐ 4☐ 5☐ 6☐ 7☐

15 a. On a typical *week* day (or working day), how many cups of tea would you drink?	1☐ 2☐ 3☐ 4☐ 5☐6☐ 7☐ 8☐ 9☐ 10☐more than 10☐
15 b. On a typical *weekend* day (or non-working day), how many cups of tea would you drink?	1☐ 2☐ 3☐ 4☐ 5☐6☐ 7☐ 8☐ 9☐ 10☐more than 10☐

16. How has having a liver condition affected your tea drinking? Please tick ONE of the answers below	
I drink a lot less tea now	☐
I drink slightly less tea now	☐
My tea drinking has not changed	☐
I drink slightly more tea now	☐
I drink a lot more tea now	☐

17. Have you ever been advised to change your tea drinking by a healthcare professional? (Tick all that apply)	
No	☐
Yes, advised to drink less tea	☐
Yes, advised to drink more tea	☐

18. What type of tea do you drink the most often? (Does not include fruit teas)		
Normal (black leaf tea eg. English Breakfast, Earl Grey, Darjeeling, PG Tips, Tetley etc)	☐	
Green tea (includes flavoured green teas)	☐	
Other - Please state:		

19. Is the tea you drink most often caffeinated or decaffeinated?			
Caffeinated	☐	Decaffeinated	☐

20. What size tea cup/mug do you use the most often?			
S (Home cup) 	☐	L (Coffee/tea shop Large) 	☐
S+ (Home mug) 	☐	XL (Coffee/tea shop Extra Large) 	☐
M (Coffee/tea shop Medium/Regular) 	☐		

21. What type of milk, if any, do you usually add to your tea?			
None	☐	Semi-skimmed	☐
Skimmed milk	☐	Full-fat	☐
Cream	☐	I'm not sure	☐

22. What type of additional sweetness, if any, do you usually add to your tea?			
None	☐	Artificial sweetener	☐
Sugar	☐		
Other - Please state:			

23. Where do you drink your tea? (Tick all that apply)			
Home	☐	Coffee shop or cafe	☐
Work	☐	Restaurant	☐
Other - Please state:			

Please now move onto section 3 on the next page

Section 3

COLA

24. Do you drink cola (with caffeine) <u>at least once a week</u>? (includes Coca cola, Pepsi, own brand, Dr Pepper, cola mixed with alcohol)			
Yes	☐	No (Please now go to section 4 'energy drinks' on page 9)	☐

25. In a <u>typical week</u> how many <u>days</u> would you drink cola?	1☐ 2☐ 3☐ 4☐ 5☐ 6☐ 7☐

26 a. On a <u>typical *week* day (or working day),</u> how many <u>times</u> would you drink cola?	1☐2☐ 3☐ 4☐ 5☐ 6☐ 7☐ 8☐ 9☐ 10☐ more than 10☐
26 b. On a <u>typical *weekend* day (or non-working day),</u> how many <u>times</u> would you drink cola?	1☐2☐ 3☐ 4☐ 5☐ 6☐ 7☐ 8☐ 9☐ 10☐ more than 10☐

27. How has having a liver condition affected your cola drinking? Please tick ONE of the answers below	
I drink a lot less cola now	☐
I drink slightly less cola now	☐
My cola drinking has not changed	☐
I drink slightly more cola now	☐
I drink a lot more cola now	☐

28. Have you ever been advised to change your cola drinking by a healthcare professional? (tick all that apply)	
No	☐
Yes, advised to drink less cola	☐
Yes, advised to drink more cola	☐

29. What type of cola do you drink most often?			
Regular cola (includes Coca cola, Pepsi cola, own brand cola, Dr Pepper)	☐	Diet cola (includes Coca cola, Pepsi cola, own brand cola, Dr Pepper)	☐
Other - Please state:			
30. What size cola can/bottle/glass do you use the most often?			
S (small glass) 	☐	L (Large glass / 500ml bottle) 	☐
SM (Half-pint glass) 	☐	XL (Pint glass) 	☐
M (Medium glass / 330ml can) 	☐		
31. Where do you drink your cola? (Tick all that apply)			
Home	☐	Coffee shop or cafe	☐
Work	☐	Restaurant	☐
Bar/pub	☐	Gym/sports centre	☐
Cinema/theatre	☐		
Other - Please state:			

Please now move onto section 4 on the next page

Section 4

ENERGY DRINKS

32. Do you drink energy drinks <u>that contain caffeine</u> <u>at least once a week</u>?			
Yes	☐	No (Please now go to section 5 'Drinking more coffee' on page 11)	☐

33. In a <u>typical week</u> how many <u>days</u> would you drink energy drinks?	1☐ 2☐ 3☐ 4☐ 5☐ 6☐ 7☐

34 a. On a <u>typical *week* day (or working day),</u> how many <u>times</u> would you drink energy drinks?	1☐ 2☐ 3☐ 4☐ 5☐ 6☐ 7☐ 8☐ 9☐ 10☐ more than 10☐
34 b. On a <u>typical *weekend day* (or non-working day),</u> how many <u>times</u> would you drink energy drinks?	1☐ 2☐ 3☐ 4☐ 5☐ 6☐ 7☐ 8☐ 9☐ 10☐ more than 10☐

35. How has having a liver condition affected your energy drinks drinking? Please tick ONE of the answers below	
I drink a lot less energy drinks now	☐
I drink slightly less energy drinks now	☐
My energy drinks drinking has not changed	☐
I drink slightly more energy drinks now	☐
I drink a lot more energy drinks now	☐

36. Have you ever been advised to change your energy drinks drinking by a healthcare professional? (Tick all that apply)	
No	☐
Yes, advised to drink less energy drinks	☐
Yes, advised to drink more energy drinks	☐

37. What type of energy drinks do you drink most often?			
Emerge	☐	Red Bull	☐
Lucozade energy	☐	Relentless	☐
Monster	☐	Rockstar	☐
Mountain Dew	☐	Unsure of brand	☐
Other - Please state:			

38. What size energy drink can/bottle/glass do you use the most often?			
S (250ml can) 	☐	L (500ml can/bottle) 	☐
S+ (Half pint glass) 	☐	XL (Pint Glass) 	☐
M (330ml can) 	☐		

39. Where do you drink your energy drinks? (Tick all that apply)			
Home	☐	Coffee shop or cafe	☐
Work	☐	Restaurant	☐
Bar/pub	☐	Gym/sports centre	☐
Cinema/theatre	☐		
Other - Please state:			

Please now move onto section 5 on the next page

Section 5

Drinking more coffee

Please complete this section even if you do not currently drink any coffee

40. What is your view about whether coffee is beneficial or harmful to <u>health in general</u>? (not including pregnancy)	**Very beneficial to health**	☐
	Slightly beneficial to health	☐
	No effect on health	☐
	Slightly harmful to health	☐
	Very harmful to health	☐
	Not sure	☐

41. What is your view about whether coffee is beneficial or harmful to the <u>health of your liver</u>?	**Very beneficial to liver health**	☐
	Slightly beneficial to liver health	☐
	No effect on liver health	☐
	Slightly harmful to liver health	☐
	Very harmful to liver health	☐
	Not sure	☐

42. If a healthcare professional advised you to drink two extra cups of <u>caffeinated</u> coffee each day to help your liver, do you think you would be able to achieve this?	**Yes**	☐ **(Please now move onto the next page and answer Q44)**
	No	☐ **(Please now move onto the next page and answer Q43)**

Question 43 is on the next page

43. What would be your main reason(s) for not being able to drink more caffeinated coffee? **Tick all that apply**	**Too expensive**	☐
	Not enough time	☐
	I do NOT like the taste of coffee	☐
	It would affect my sleep	☐
	I would feel generally unwell	☐
	My heart would race	☐
	I would get headache (including migraine)	☐
	It would cause anxiety	☐
	It would cause tremor	☐
	I would need the toilet too much	☐
	I would feel too dehydrated	☐
	Other – please state: **_____**	☐

44. If a healthcare professional advised you to drink two extra cups of <u>decaffeinated</u> coffee each day to help your liver, do you think you would be able to achieve this?	**Yes**	☐
	No	☐

Please now move onto section 6 on the next page

Section 6

Your views on further research

Please complete this section even if you do not currently drink any coffee

45. Imagine a research study to investigate the effects of coffee drinking on the liver. If the study was to ask one group of participants to drink <u>two extra cups of caffeinated coffee each day</u>, and the other group to drink their usual coffee, do you think this would be acceptable?	**Yes**	☐
	No	☐
	Not sure **Please state reason:** **_____** **_____**	☐

46. If each person taking part in the study had an equal chance of ending up in either group, do you think this would be acceptable?	**Yes**	☐
	No	☐
	Not sure **Please state reason:** **_____** **_____**	☐

Question 47 is on the next page

47. Imagining you were in such a study and ended up in the <u>two extra coffee cups a day</u> group, what would you find acceptable in the way the extra coffee was organised? **(Please tick all the answers you would find acceptable)**	**Drink more of your own coffee at your own expense**	☐
	Given a fixed allowance towards paying for any type of coffee you choose to make up the extra two cups	☐
	Given the extra coffee in the form of instant coffee sachets	☐
	Given the extra coffee in the form of freshly ground coffee and a suitable device to brew it	☐
	Not sure	☐
	Other: Please state	☐

48. Again imagining you were in such a research study that lasted two years, would you find it acceptable to have blood tests at the start, and repeated every 6 months, for the duration of the study.	**Yes**	☐
	No	☐
	Not sure **Please state reason:** **_____** **_____**	☐

49. Again imagining you were in such a research study that lasted two years, would you find it acceptable to have a liver scan at the start, and repeated twice during the study.	**Yes**	☐
	No	☐
	Not sure **Please state reason:** **_____** **_____**	☐

50. Again imagining you were in such as study, what extra help, if any, do you think you would need in order to remember to drink those extra two coffee cups each day?	**None**	☐
	Text message reminders	☐
	Email reminders	☐
	Other – please state:	☐

51. Imagining you were invited to take part in this type of study, would you be interested? **(This is a hypothetical question – you will not be contacted based on your response)**	**Yes**	☐
	No	☐
	Not sure	☐

Please now move onto section 7 below

Section 7

About you

We ask you some additional questions in this section so we can learn more about the different backgrounds of people taking part in our coffee survey and to ensure that we have asked a good range of people. Your answers will remain anonymous.

52. What is you gender?	**Male**	☐
	Female	☐

Question 53 is on the next page

53. What is your age group?	**18-24**	☐
	25-34	☐
	35-44	☐
	45-54	☐
	55-64	☐
	65-74	☐
	75-84	☐
	85+	☐

54. What is your ethnicity? (Please tick)	**White**	**British**	☐
		Irish	☐
		Other	☐
	Mixed	**White & Asian**	☐
		White & Black African	☐
		White & Black Caribbean	☐
		Any other mixed background	☐
	Chinese		☐
	Asian or Asian British	**Bangladeshi**	☐
		Indian	☐
		Pakistani	☐
		Any other Asian background	☐
	Black or Black British	**African**	☐
		Caribbean	☐
		Any other black background	☐
	Other ethnicity		

55. What is your employment status?	**Paid employment or self-employed**	☐
	Retired	☐
	Looking after home and/or family	☐
	Unable to work because of sickness or disability	☐
	Unemployed	☐
	Doing unpaid or voluntary work	☐
	Full or part-time student	☐
	None of the above	☐
	Prefer not to answer	☐

56. Do you own or rent your accommodation?	**Own outright (you or someone in your household)**	☐
	Own with a mortgage	☐
	Rent from local authority, local council, or housing association	☐
	Rent from private landlord or letting agency	☐
	Pay part rent and part mortgage (shared ownership)	☐
	Live in accommodation rent free	☐
	None of the above	☐
	Prefer not to answer	☐

57. <u>Including yourself</u>, how many people are living together in your household? **(If you live alone, enter '1')**	

Question 58 is on the next page

58. What is your height (to the nearest unit measurement) in feet and inches, or metres?		**FEET**		**INCHES**
	or			
		M		**Cm**

59. What is your weight (to the nearest unit measurement) in stone or kilograms?		**STONE**
	or	
		Kilograms

60. Have you ever been diagnosed as having heart disease?	**Yes**	☐
	No	☐

61. Have you ever been diagnosed as having had a stroke?	**Yes**	☐
	No	☐

62. Have you ever been diagnosed as having type II diabetes?	**Yes**	☐
	No	☐

63. Do you smoke cigarettes?	**Yes**	☐
	No (now move to Q 65)	☐

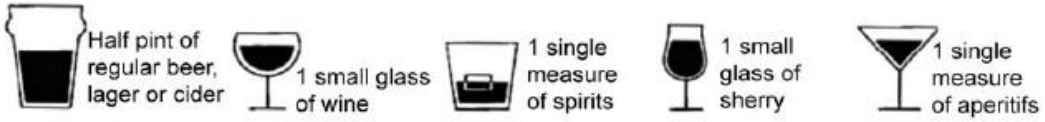
64. How many cigarettes do you smoke each day?	**0-9**	☐
	10-19	☐
	≥20	☐

65. Do you use e-cigarettes?	**Yes**	☐
	No	☐

Question 66 is on the next page

Q66 to 68 refer to alcohol. Please use the following as a guide

This is one unit of alcohol…



…and each of these is more than one unit

66. How often do you have a drink containing alcohol? (please choose one)	**Never**	☐
	Monthly or less	☐
	2-4 times per month	☐
	2-3 times per week	☐
	4-5 times per week	☐
	6-7 times per week	☐

67. How many units of alcohol do you drink on a typical day when you are drinking? Refer to the chart above if needed	**1-2**	☐
	3-4	☐
	5-6	☐
	7-9	☐
	10+	☐

68. How often have you had 6 or more units if female, or 8 or more if male, on a single occasion in the last year?	**Never**	☐
	Less than monthly	☐
	Monthly	☐
	Weekly	☐
	Daily or almost daily	☐

69. Do you take any additional medication or supplements that contain caffeine (at least once a week, most weeks)	**Yes** **Please state type and how often:** _____ _____	☐
	No	☐

You have reached the end of the questionnaire.

Thank you very much for taking the time to complete it.

<u>Please now place the questionnaire in the accompanying pre-paid envelope and post back to the research team.</u>

Your answers will help us understand more about patterns of coffee drinking in people with liver conditions and help us plan further research to help people in the future

Appendix L CUPLID postal survey reminder letter

University Hospital Southampton NHS
NHS Foundation Trust

UNIVERSITY OF Southampton

Department of Hepatology
University Hospital Southampton NHS Foundation Trust
Tremona Road
Southampton
SO16 6YD

Date to be inserted

«Skip Record If…»«Title» «Forename» «Surname»
«Address_Line_1»
«Address_Line_2»
«Address_Line_3»
«County»
«Postcode»

Dear «Title» «Surname»

We recently sent you a questionnaire about research we are undertaking to understand more about coffee drinking in people with liver conditions, views about increasing coffee intake, and opinion about further research that we may do in the future. This is because existing studies suggests coffee drinking *might* be good for liver health but we need to do more research to be sure. So, whether you like coffee or dislike coffee, we need you!

Taking part is completely optional but in case you did not receive the previous questionnaire, we have enclosed another copy. The questionnaire should take approximately 15 minutes to complete.

Your answers will **remain entirely anonymous**. There is however a unique code attached to each questionnaire that will help us monitor which questionnaires have been returned.

If you would like to take part, we would be very grateful if you would complete the questionnaire and return it to us in the pre-paid envelope.

We are very grateful for your participation. However, if you decide not to respond to this invitation, we will **not** contact you again.

Yours sincerely

Dr Consultant Name
Consultant Hepatologist

The research is a collaboration between University Hospital Southampton and the University of Southampton Primary Care and Population Science Academic Unit and has full NHS ethical approval (no: 17/WS/0231). The research team will **not** have access to any of your personal information. **If you would like to understand more about the research then please read the accompanying participant information sheet.** If you would like to know how personal information is used by the NHS for purposes of health research, then please visit: https://www.hra.nhs.uk/information-about-patients/

Appendix M Coffee units/mL used in CUPLID survey to convert coffee cups to coffee units

Table 47: Coffee units per mL used to convert coffee cup data to coffee unit data

Coffee preparation type	Coffee units/mL coffee consumed
Instant	0.84
Decaffeinated instant	0.46
Filter	1.43
Decaffeinated filter	0.75
Cafetière	1.17
Capsule/pod	1.13
Cappuccino	1.13
Latte	1.13
Decaffeinated latte	0.39
Flat white	1.13
Americano	1.13
Mocha	1.13
Single espresso	4.75
Double espresso	4.75

Appendix N Regular and day before coffee consumption quantification

Table 48: Quantification of regular coffee consumption

	Median days in week drinking coffee (IQR)	Median cups a day week or working day (IQR)	Median cups a day weekend or non-working day (IQR)
Any coffee drinker (n=303)	7.0 (4.0 to 7.0)	2.0 (1.0 to 4.0)	2.0 (1.0 to 4.0)
Caffeinated coffee drinker	7.0 (5.0 to 7.0)	2.0 (1.0 to 4.0)	2.0 (1.0 to 3.0)
Decaffeinated coffee drinker	7.0 (3.0 to 7.0)	2.0 (1.0 to 3.3)	1.0 (1.0 to 1.0)

Table 49: Quantification of coffee consumption day before completing questionnaire

	Median number of types yesterday (IQR)	Median cups yesterday (IQR)	Median coffee units yesterday (IQR)
Any coffee drinker (n=274)	1.0 (1.0 to 1.0)	2.0 (1.0 to 3.0)	2.7 (1.3 to 4.0)
Caffeinated coffee drinker	1.0 (1.0 to 1.0)	2.0 (1.0 to 3.0)	2.7 (1.5 to 4.5)
Decaffeinated coffee drinker	1.0 (1.0 to 1.0)	2.0 (1.0 to 3.0)	1.1 (0.5 to 2.1)

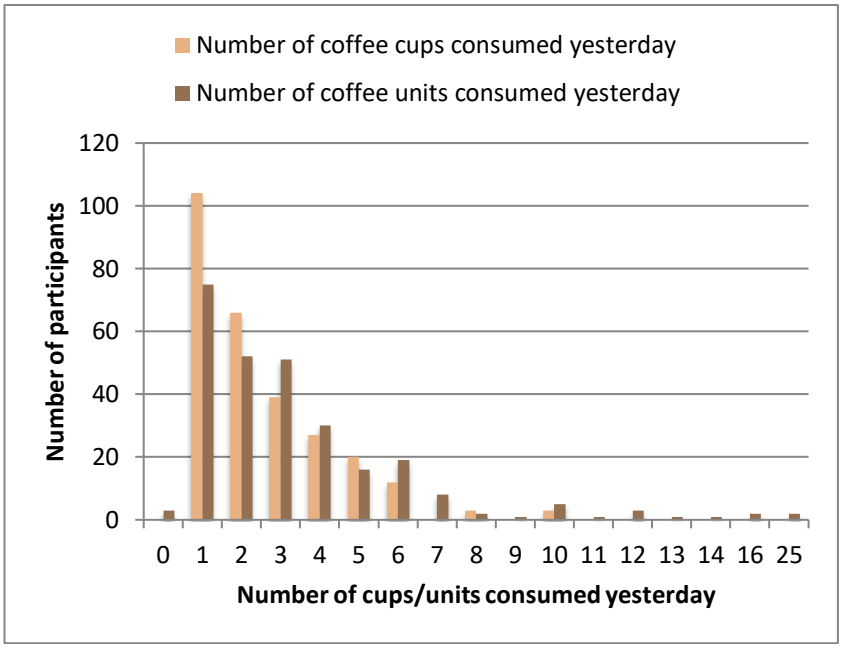


Figure 41: The number of coffee cups and units consumed the day before questionnaire

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Table 50: Coffee preparation types consumed the day before questionnaire for caffeinated coffee

Caffeinated Coffee preparation	Participants consuming type yesterday		Cups consumed yesterday		Median number of cups consumed yesterday	Range of cups consumed yesterday	
	N	%	N	%		Lower	Upper
Any caffeinated coffee	234	100	594	100	2.0 (1.0 to 3.0)	1	10
Instant	139	59.4	352	59.3	2.0 (1.0 to 4.0)	1	10
Cafè Latte	36	15.4	53	8.9	1.0 (1.0 to 2.0)	1	6
Filter	24	10.3	42	7.1	1.5 (1.0 to 2.0)	1	4
Capsule/pod	27	11.5	51	8.6	1.0 (1.0 to 2.0)	1	5
Cappuccino	18	7.7	29	4.9	1.0 (1.0 to 2.0)	1	6
Americano	13	5.6	16	2.7	1.0 (1.0 to 1.0)	1	3
Flat White	11	4.7	15	2.5	1.0 (1.0 to 2.0)	1	3
Cafetière	10	4.3	17	2.9	2.0 (1.0 to 2.0)	1	3
Mocha	6	2.6	9	1.5	1.0 (1.0 to 2.3)	1	3
Single espresso	5	2.1	8	1.3	1.0 (1.0 to 2.5)	1	4
Double espresso	2	0.9	2	0.3	1.0 (1.0 to 1.0)	1	1

Table 51: Coffee preparation types consumed the day before questionnaire for decaffeinated coffee

Decaffeinated Coffee preparation	Participants consuming type yesterday		Cups consumed yesterday		Median number of cups consumed yesterday	Range of cups consumed yesterday	
	N	%	N	%		Lower	Upper
Any decaffeinated coffee	39	100	86	100	2.0 (1.0 to 3.0)		
Instant	30	76.9	64	74.4	1.5 (1.0 to 3.0)	1	8
Cafè Latte	5	12.8	8	9.3	1.0 (1.0 to 2.5)	1	3
Filter	5	12.8	7	8.1	1.0 (1.0 to 2.0)	1	2
Capsule/pod	2	5.1	2	2.3	1.0 (1.0 to 1.0)	1	1
Cappuccino	1	2.6	1	1.2	1.0 (1.0 to 1.0)	1	1
Americano	2	5.1	3	3.5	1.5 (1.3 to 1.8)	1	2
Flat White	1	2.6	1	1.2	1.0 (1.0 to 1.0)	1	1
Cafetière	0	0.0	0	0.0	0	0	0
Mocha	0	0.0	0	0.0	0	0	0
Single espresso	0	0.0	0	0.0	0	0	0
Double espresso	0	0.0	0	0.0	0	0	0

Table 52: Number of preparation types consumed at least once a week

Number of preparation types regularly consumed	Number of participants any coffee		Number participants caffeinated coffee		Number of participants decaffeinated coffee	
	N	%	N	%	N	%
1	170	55.9	137	53.7	31	67.4
2	90	29.6	78	30.6	11	23.9
3	32	10.5	28	11.0	4	8.7
4	6	2.0	6	2.4	0	0.0
5	4	1.3	4	1.6	0	0.0
6	2	0.7	2	0.8	0	0.0

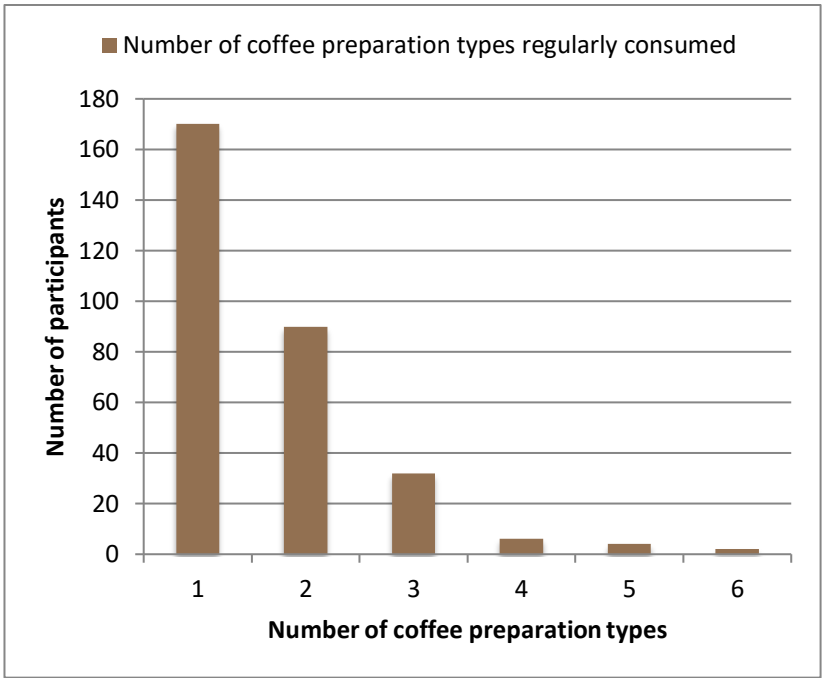

Figure 42: Number of coffee preparation types consumed regularly

Appendix O Ingredients added to coffee

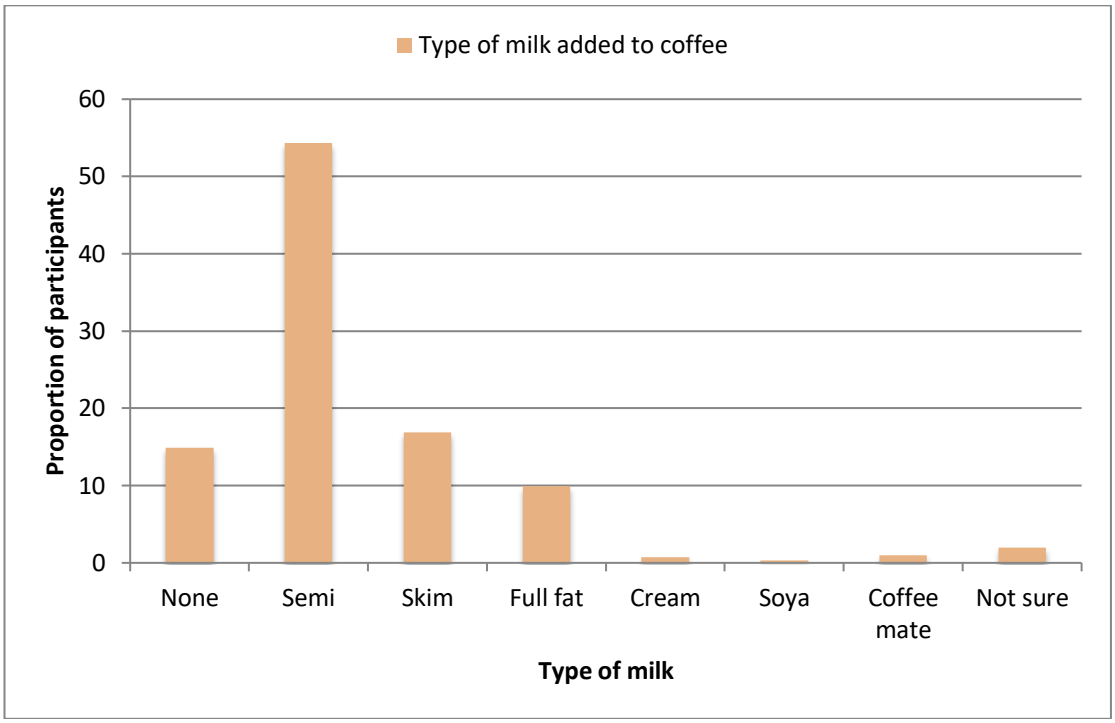

Figure 43: Type of milk added to coffee

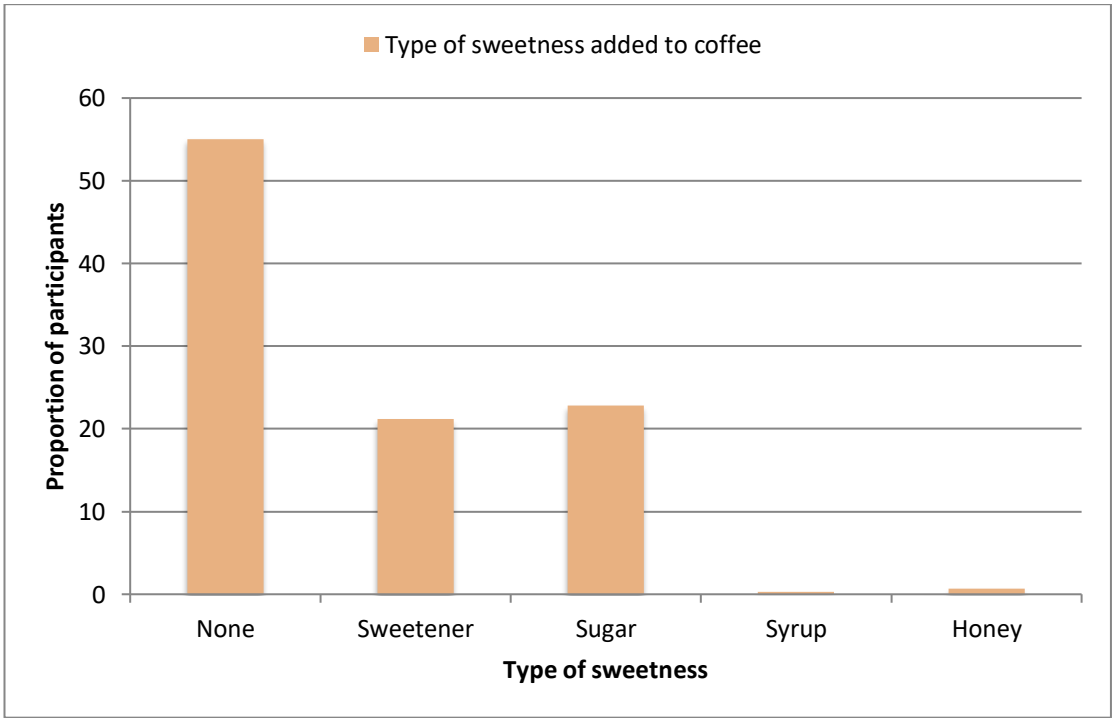

Figure 44: Type of sweetness added to coffee

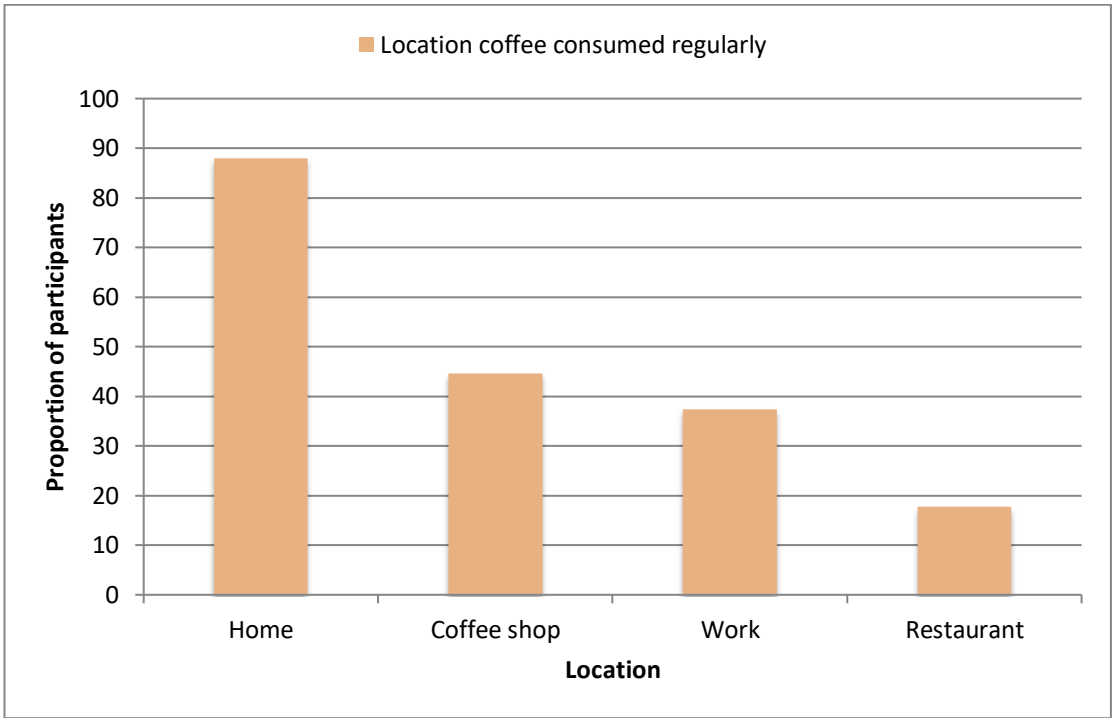

Figure 45: Location of regular coffee consumption

Appendix P Ingredients added to tea

Table 53: Additional ingredients regularly added to tea and location of consumption

Ingredients added to tea		Participants drinking any tea	
		N	%
Milk added	None	36	11.5
	Semi	172	55.1
	Skim	73	23.4
	Full fat	22	7.1
	Cream	2	0.6
	Soya	3	1.0
	Not sure	4	1.3
Sugar added	None	199	64.0
	Sweetener	57	18.3
	Sugar	54	17.4
	Other	1	0.3
Locations consumed	Home	303	97.1
	Coffee shop	74	23.7
	Work	107	35.3
	Restaurant	36	11.5

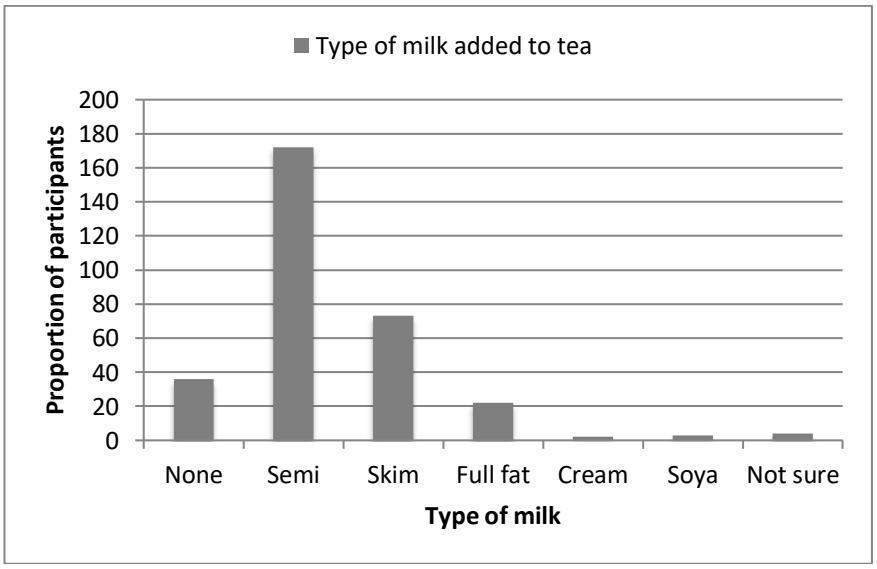

Figure 46: Type of milk added to tea

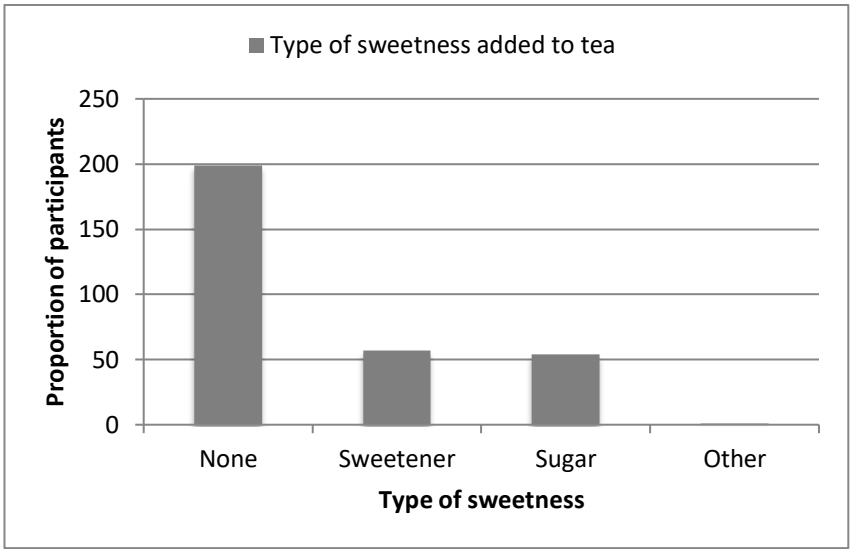

Figure 47: Type of sweetness added to tea

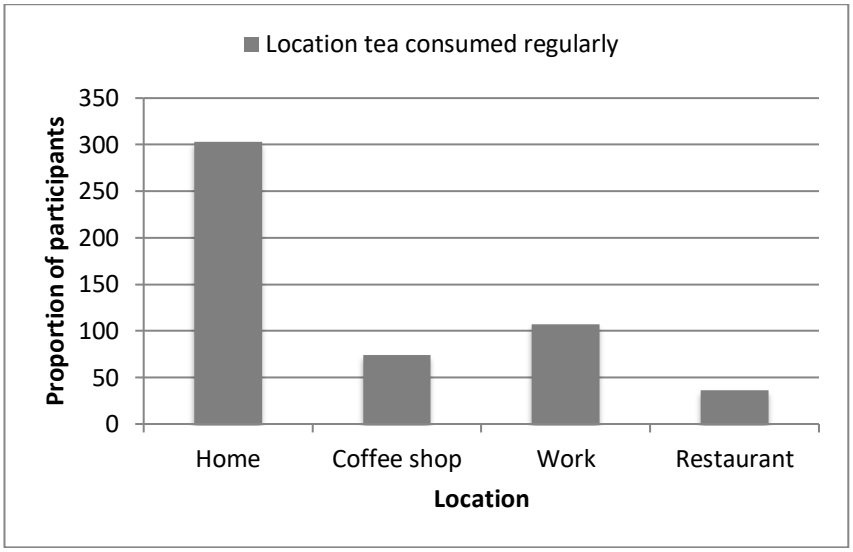

Figure 48: Location of regular tea consumption

Appendix Q Views about coffee and heath by gender, liver stiffness, age and NHS site

Table 54: Views about coffee and health by gender and liver stiffness

Characteristic		Male		Female		Liver stiffness <7 KPa		Liver stiffness 7-13 KPa		Liver stiffness >13 KPa	
		N	%	N	%	N	%	N	%	N	%
Coffee drinking since the liver condition	A lot less	11	6.0	6	5.2	3	2.4	8	8.0	6	8.3
	Slightly less	10	5.5	4	3.5	7	5.5	4	4.0	3	4.2
	Not	135	73.8	91	79.1	101	79.5	74	74.0	52	72.2
	Slightly	21	11.5	10	8.7	11	8.7	12	12.0	8	11.1
	A lot more	6	3.3	4	3.5	5	3.9	2	2.0	3	4.2
Healthcare professional advice to change coffee intake	No	155	83.8	102	87.9	111	86.0	85	77.3	63	86.3
	Drink less	4	2.2	7	6.0	5	3.9	5	4.5	1	1.4
	Drink more	24	13.0	7	6.0	12	9.3	19	17.3	9	12.3
	Less &	2	1.1	0	0.0	1	0.8	1	0.9	0	0.0
Coffee and general health	Very	12	5.4	4	2.5	6	4.0	6	4.5	4	3.9
	Beneficial	34	15.4	25	15.4	24	16.0	22	16.4	13	12.7
	No effect	49	22.2	34	21.0	38	25.3	28	20.9	18	17.6
	Harmful	28	12.7	21	13.0	20	13.3	17	12.7	12	11.8
	Very	3	1.4	2	1.2	2	1.3	2	1.5	1	1.0
	Unsure	95	43.0	76	46.9	60	40.0	59	44.0	54	52.9
Coffee and liver health	Very	7	3.2	8	5.0	6	4.0	5	3.7	4	4.0
	Beneficial	30	13.6	14	8.8	16	10.7	19	14.2	9	8.9
	No effect	45	20.4	35	21.9	33	22.1	32	23.9	15	14.9
	Harmful	13	5.9	10	6.3	5	3.4	11	8.2	7	6.9
	Very	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Unsure	126	57.0	93	58.1	89	59.7	67	50.0	66	65.3

Table 55: Views about coffee and health by age group

Characteristic		Age 25-34		Age 35-44		Age 45-54		Age 55-64		Age 65-74		Age 75-84	
		N	%	N	%	N	%	N	%	N	%	N	%
Coffee drinking since the liver condition	A lot less	2	18.2	0	0.0	3	4.9	5	4.6	5	6.3	2	8.3
	Slightly less	0	0.0	1	6.7	3	4.9	4	3.7	6	7.6	0	0.0
	Not	5	45.5	11	73.3	46	75.4	86	79.6	61	77.2	18	75.0
	Slightly	3	27.3	1	6.7	9	14.8	9	8.3	6	7.6	3	12.5
	A lot more	1	9.1	2	13.3	0	0.0	4	3.7	1	1.3	1	4.2
Healthcare professional advice to change coffee intake	No	6	54.5	12	80.0	56	88.9	92	84.4	70	87.5	22	91.7
	Drink less	2	18.2	1	6.7	2	3.2	5	4.6	1	1.3	0	0.0
	Drink more	3	27.3	2	13.3	5	7.9	10	9.2	9	11.3	2	8.3
	Less &	0	0.0	0	0.0	0	0.0	2	1.8	0	0.0	0	0.0
Coffee and general health	Very	3	27.3	1	4.8	2	2.8	4	2.9	3	2.9	3	8.6
	Beneficial	2	18.2	3	14.3	13	18.1	26	18.7	13	12.4	2	5.7
	No effect	2	18.2	4	19.0	17	23.6	26	18.7	26	24.8	8	22.9
	Harmful	2	18.2	4	19.0	10	13.9	24	17.3	6	5.7	3	8.6
	Very	0	0.0	0	0.0	1	1.4	3	2.2	1	1.0	0	0.0
	Unsure	2	18.2	9	42.9	29	40.3	56	40.3	56	53.3	19	54.3
Coffee and liver health	Very	2	18.2	1	4.8	2	2.8	4	2.9	3	2.9	3	8.6
	Beneficial	2	18.2	1	4.8	10	13.9	17	12.3	13	12.5	1	2.9
	No effect	1	9.1	6	28.6	13	18.1	36	26.1	15	14.4	9	25.7
	Harmful	1	9.1	3	14.3	4	5.6	11	8.0	4	3.8	0	0.0
	Very	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Unsure	5	45.5	10	47.6	43	59.7	70	50.7	69	66.3	22	62.9

Table 56: Views about coffee and health by NHS site

Characteristic		All sites		University Hospital Southampton		Queen Alexandra Hospital		Royal Infirmary of Edinburgh			
		N	%	N	%	N	%	N	%	N	%
Coffee drinking since the liver condition (n=300)	A lot less	17	5.7	10	8.9	5	4.0	2	3.1		
	Slightly less	14	4.7	4	3.6	7	5.6	3	4.7		
	Not changed	228	76.0	88	78.6	106	85.5	34	53.1		
	Slightly	31	10.3	5	4.5	5	4.0	21	32.8		
	A lot more	10	3.3	5	4.5	1	0.8	4	6.3		
Healthcare professional advice to change coffee intake	No	260	85.5	105	91.3	121	96.8	34	53.1		
	Drink less	11	3.6	7	6.1	3	2.4	1	1.6		
	Drink more	31	10.2	2	1.7	1	0.8	28	43.8		
	Less & More	2	0.7	1	0.9	0	0	1	1.6		
Coffee and general health	Very	16	4.1	4	2.8	5	3.0	7	8.8		
	Beneficial	59	15.2	18	12.6	22	13.4	19	23.8		
	No effect	84	21.7	32	22.4	39	23.8	13	16.3		
	Harmful	49	12.7	21	14.7	22	13.4	6	7.5		
	Very harmful	5	1.3	3	2.1	2	1.2	0	0.0		
	Unsure	174	45.0	65	45.5	74	45.1	35	43.8		
Coffee and liver health	Very	15	3.9	3	1.5	3	1.3	9	7.5		
	Beneficial	44	11.4	9	4.5	11	4.8	24	20.0		
	No effect	80	20.8	35	17.5	39	17.2	6	5.0		
	Harmful	23	6.0	10	5.0	12	5.3	1	0.8		
	Very harmful	0	0	0	0.0	0	0.0	0	0.0		
	Unsure	223	57.9	143	71.5	162	71.4	80	66.7		

Appendix R Achievability of drinking more coffee by gender, liver stiffness, age and NHS site

Table 57: Views about achievability of drinking more coffee by gender and liver stiffness

Characteristic		Male		Female		Liver		Liver		Liver	
		N	%	N	%	N		N	%	N	%
Could drink 2 more cups caffeinated coffee	Yes	187	85.8	113	70.2	113	76.4	109	81.3	80	80.0
	No	31	14.2	47	29.2	35	23.6	25	18.7	19	19.0
	Unsure	0	0.0	1	0.6	0	0.0	0	0.0	1	1.0
Reasons for not being able to drink more caffeinated coffee	Expense	4	6.2	2	2.6	1	1.7	4	6.9	2	7.4
	Time	3	4.6	1	1.3	3	5.0	0	0.0	1	3.7
	Taste	9	13.8	25	32.1	12	20.0	15	25.9	8	29.6
	Sleep	13	20.0	12	15.4	13	21.7	10	17.2	2	7.4
	Unwell	4	6.2	4	5.1	3	5.0	4	6.9	1	3.7
	Heart	5	7.7	4	5.1	4	6.7	3	5.2	2	7.4
	Headache	4	6.2	11	14.1	7	11.7	5	8.6	3	11.1
	Anxiety	2	3.1	3	3.8	3	5.0	2	3.4	0	0.0
	Tremor	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Toilet	17	26.2	12	15.4	10	16.7	13	22.4	6	22.2
	Dehydration	4	6.2	4	5.1	4	6.7	2	3.4	2	7.4
Could drink 2 more cups de-caffeinated coffee	Yes	179	84.8	116	70.7	116	80.6	106	80.3	75	73.5
	No	31	14.7	45	27.4	28	19.4	24	18.2	25	24.5
	Unsure	1	0.5	3	1.8	0	0.0	2	1.5	2	2.0

Table 58: Views about achievability of drinking more coffee by age

		Age 25-34		Age 35-44		Age 45-54		Age 55-64		Age 65-74		Age 75-84	
		N	%	N	%	N	%	N	%	N	%	N	%
Could drink 2 more cups caffeinated coffee	Yes	10	90.9	15	75.0	59	81.9	113	81.3	79	76.0	25	75.8
	No	1	9.1	5	25.0	13	18.1	25	18.0	25	24.0	8	24.2
	Unsure	0	0.0	0	0.0	0	0.0	1	0.7	0	0.0	0	0.0
	Time	2	50.0	0	0.0	1	3.4	1	2.1	0	0.0	0	0.0
	Taste	0	0.0	3	27.3	4	13.8	14	29.8	10	25.0	3	23.1
	Sleep	0	0.0	2	18.2	6	20.7	8	17.0	7	17.5	2	15.4
	Unwell	0	0.0	2	18.2	1	3.4	1	2.1	3	7.5	1	7.7
	Heart	0	0.0	1	9.1	2	6.9	3	6.4	2	5.0	1	7.7
	Headache	0	0.0	1	9.1	7	24.1	3	6.4	3	7.5	1	7.7
	Anxiety	0	0.0	0	0.0	2	6.9	3	6.4	0	0.0	0	0.0
	Tremor	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Toilet	1	25.0	1	9.1	4	13.8	9	19.1	9	22.5	5	38.5
	Dehydration	1	25.0	0	0.0	2	6.9	4	8.5	1	2.5	0	0.0
	Other												
Could drink 2 more cups de-caffeinated coffee	Yes	8	72.7	14	73.7	61	87.1	109	79.0	77	75.5	27	77.1
	No	3	27.3	5	26.3	9	12.9	27	19.6	24	23.5	7	20.0
	Unsure	0	0.0	0	0.0	0	0.0	2	1.4	1	1.0	1	2.9

Table 59: Views about achievability of drinking more coffee by NHS site

Could drink 2 more cups caffeinated coffee	Yes	302	78.9	111	77.6	127	79.4	64	80.0		
	No	80	20.9	32	22.4	32	20.0	16	20.0		
	Not sure	1	0.3	0	0.0	1	0.6	0	0.0		
Reasons for not being able to drink more caffeinated coffee	Expense	4	3.8	3	5.0	2	3.7	3	9.4		
	Time	2	1.9	1	1.7	2	3.7	1	3.1		
	Taste	34	32.1	12	20.0	15	27.8	8	25.0		
	Sleep	16	15.1	12	20.0	7	13.0	6	18.8		
	Unwell	7	6.6	3	5.0	2	3.7	3	9.4		
	Heart racing	6	5.7	6	10.0	1	1.9	2	6.3		
	Headache	11	10.4	7	11.7	6	11.1	2	6.3		
	Anxiety	5	4.7	2	3.3	2	3.7	1	3.1		
	Tremor	0	0.0	0	0.0	0	0.0	0	0.0		
	Toilet	16	15.1	10	16.7	14	25.9	5	15.6		
	Dehydration	5	4.7	4	6.7	3	5.6	1	3.1		
Could drink 2 more cups de-caffeinated coffee	Yes	297	78.4	113	80.1	128	78.5	56	74.7		
	No	78	20.6	28	19.9	33	20.2	17	22.7		
	Not sure	4	1.1	0	0.0	2	1.2	2	2.7		

Table 60: Achievability of drinking two additional cups of caffeinated coffee by socio-demographic, behavioural and clinical subgroups, with % instant coffee intake

	Could achieve drinking 2 more cups caffeinated coffee if advised by health professional cups			% Instant
	Y	N	Not sure	
Ethnicity White	79.8	19.9	0.3	55.5
Ethnicity Non-White	68.0	32.0	0.0	46.4
Employed or self-employed	82.0	18.0	0.0	50.8
Retired	78.1	21.9	0.0	55.7
Other employment category	71.2	27.1	0.0	68.6
Owns house outright/mortgage	80.3	19.7	0.0	54.6
Public sector renting	82.8	15.6	1.6	58.2
Private sector renting	66.7	33.3	0.0	50.8
Other accommodation	70.4	29.6	0.0	59.2
Lives alone	79.0	21.0	0.0	61.6
Lives with others	78.4	20.3	1.3	53.6
Smoking	82.8	17.2	0.0	54.7
Non-smoking	78.7	21.0	0.3	59.5
Audit-C Score ≥5	82.4	17.6	0.0	52.0
Audit-C Score <5	77.6	22.1	0.4	56.6
Healthy weight status	72.0	28.0	0.0	42.8
Overweight weight status	84.7	15.3	0.0	48.1
Obese weight status	78.0	21.5	0.5	60.8
Comorbidity of diabetes	79.9	19.5	0.6	55.3
Comorbidity of CHD	78.5	20.0	1.5	56.5
Comorbidity of Stroke	73.3	26.7	0.0	85.4

Appendix S Free-text reasons for not being able to achieve an increase in caffeinated coffee intake

Table 61: Free text reasons for not being able to achieve an increase in two cups of caffeinated coffee a day

Reason
All my life I have drunk cold water as my main drink. I have coffee at breakfast and the occasional social cup with friends. I prefer cold drinks and there are no calories in H20 and it is good for your skin! I feel I would struggle to drink that much coffee every day and would probably forget to do so as hot drinks are not habitual.
Already drink about three a day
Habit
Have been told its bad for you so don't drink it
Heartburn
I already drink a lot of coffee
I am not a guinea pig
I don't drink coffee kicks my IBS off
I don't drink lots of coffee/tea
I don't like coffee
I don't like the smell
I drink milky coffee only to settle my stomach on the morning
I enjoy the taste but it leaves an unpleasant aftertaste after 20-30 minutes
I like drinking water too
I prefer tea
I prefer tea or orange juice or water
I would be sick
I would feel sick
Is not healthcare for me
Like it weaker - if more latte would be too much milk
No reason
Not keen on it
Palpitations
Stomach Ache
Would make me feel hyperactive

d

Appendix T Research acceptability, design, and assistance

Table 62: Research acceptability, design, and assistance by gender and liver stiffness

Characteristic		Male		Female		Liver stiffness <7 KPa		Liver stiffness 7-13 KPa		Liver stiffness >13 KPa	
		N	%	N	%	N	%	N	%	N	%
Intervention acceptable (2 extra cups of coffee each day versus usual intake)	Yes	195	89.0	133	81.1	126	84.0	118	88.7	86	83.5
	No	8	3.7	17	10.4	9	6.0	7	5.3	10	9.7
	Not sure	16	7.3	14	8.5	15	10.0	8	6.0	7	6.8
Randomisation acceptable (Equal chance of ending up in each group)	Yes	184	84.4	132	80.5	125	83.3	112	84.2	81	79.4
	No	12	5.5	15	9.1	11	7.3	6	4.5	11	10.8
	Not sure	22	10.1	17	10.4	14	9.3	15	11.3	10	9.8
Blood tests acceptable	Yes	202	92.7	143	87.7	137	91.9	121	92.4	89	86.4
	No	7	3.2	13	8.0	8	5.4	5	3.8	7	6.8
	Not sure	9	4.1	7	4.3	4	2.7	5	3.8	7	6.8
Liver scans acceptable	Yes	203	93.1	143	87.2	136	91.3	121	91.7	91	88.3
	No	6	2.8	11	6.7	7	4.7	5	3.8	5	4.9
	Not sure	9	4.1	10	6.1	6	4.0	6	4.5	7	6.8
How should the extra coffee be organised for the intervention group?	Own coffee	142	44.7	90	41.9	93	41.2	74	42.3	66	49.3
	Fixed	62	19.5	43	20.0	48	21.2	30	17.1	28	20.9
	Given	59	18.6	46	21.4	43	19.0	39	22.3	23	17.2
	Given	36	11.3	19	8.8	26	11.5	18	10.3	11	8.2
	Not sure	19	6.0	17	7.9	16	7.1	14	8.0	6	4.5
	Other										
Help needed to remember to take extra coffee in a research study	None	151	69.9	87	57.2	86	59.7	80	62.0	73	76.0
	Text	55	25.5	54	35.5	47	32.6	43	33.3	19	19.8
	Emails	3	1.4	4	2.6	4	2.8	3	2.3	0	0.0
	Texts &	7	3.2	1	0.7	4	2.8	1	0.8	3	3.1
	Other	0	0.0	6	3.9	3	2.1	2	1.6	1	1.0
Would you be interested in taking part in this type of study?	Yes	157	72.7	114	70.8	108	73.0	96	73.8	67	67.7
	No	27	12.5	29	18.0	26	17.6	14	10.8	16	16.2
	Not sure	32	14.8	18	11.2	14	9.5	20	15.4	16	16.2

Table 63: Research acceptability, design, and assistance by age group

Characteristic		Age 25-34		Age 35-44		Age 45-54		Age 55-64		Age 65-74		Age 75-84	
		N	%	N	%	N	%	N	%	N	%		
Intervention acceptable (2 extra cups of coffee each day versus usual intake)	Yes	11	100	20	95.2	61	87.1	129	91.5	85	81.0	22	62.9
	No	0	0.0	0	0.0	6	8.6	6	4.3	8	7.6	5	14.3
	Not sure	0	0.0	1	4.8	3	4.3	6	4.3	12	11.4	8	22.9
Randomisation acceptable (Equal chance of ending up in each group)	Yes	10	90.9	20	95.2	60	85.7	119	84.4	82	78.1	25	73.5
	No	0	0.0	0	0.0	3	4.3	12	8.5	9	8.6	3	8.8
	Not sure	1	9.1	1	4.8	7	10.0	10	7.1	14	13.3	6	17.6
Blood tests acceptable	Yes	10	90.9	20	95.2	66	94.3	129	91.5	92	87.6	28	82.4
	No	1	9.1	1	4.8	1	1.4	6	4.3	7	6.7	4	11.8
	Not sure	0	0.0	0	0.0	3	4.3	6	4.3	6	5.7	2	5.9
Liver scans acceptable	Yes	10	90.9	20	95.2	65	92.9	129	91.5	95	90.5	27	79.4
	No	0	0.0	1	4.8	1	1.4	5	3.5	6	5.7	4	11.8
	Not sure	1	9.1	0	0.0	4	5.7	7	5.0	4	3.8	3	8.8
How should the extra coffee be organised for the intervention group?	Own coffee	6	40.0	12	30.8	40	33.9	94	50.5	60	43.8	20	52.6
	Fixed	4	26.7	8	20.5	29	24.6	33	17.7	26	19.0	5	13.2
	Given	3	20.0	9	23.1	26	22.0	33	17.7	26	19.0	8	21.1
	Given	1	6.7	7	17.9	13	11.0	18	9.7	15	10.9	1	2.6
	Not sure	1	6.7	3	7.7	10	8.5	8	4.3	10	7.3	4	10.5
	Other												
Help needed to remember to take extra coffee in a research study	None	3	27.3	8	38.1	42	60.0	87	63.5	75	75.8	23	79.3
	Text	7	63.6	11	52.4	22	31.4	46	33.6	18	18.2	4	13.8
	Emails	0	0.0	0	0.0	2	2.9	2	1.5	2	2.0	1	3.4
	Texts &	1	9.1	1	4.8	3	4.3	0	0.0	2	2.0	1	3.4
	Other	0	0.0	1	4.8	1	1.4	2	1.5	2	2.0	0	0.0
Would you be interested in taking part in this type of study?	Yes	8	80.0	16	76.2	52	74.3	103	73.0	71	69.6	21	65.6
	No	1	10.0	2	9.5	8	11.4	22	15.6	17	16.7	5	15.6
	Not sure	1	10.0	3	14.3	10	14.3	16	11.3	14	13.7	6	18.8

Table 64: Hypothetical interest in taking part in a future research study by socio-demographic, behavioural and clinical subgroups with % instant coffee intake

	Would be hypothetically interested in taking part in a future research study			% Instant
	Y	N	Not sure	
Ethnicity White	71.8	15.2	13.0	55.5
Ethnicity Non-White	72.7	9.1	18.2	46.4
Employed or self-employed	75.9	12.1	12.1	50.8
Retired	68.5	17.8	13.7	55.7
Other employment category	69.0	15.5	15.5	68.6
Owns house outright/mortgage	74.1	13.9	12.0	54.6
Public sector renting	67.2	18.8	14.1	58.2
Private sector renting	65.2	13.0	21.7	50.8
Other accommodation	69.2	15.4	15.4	59.2
Lives alone	66.2	14.3	19.5	61.6
Lives with others	73.4	15.0	11.6	53.6
Smoking	82.8	10.3	6.9	54.7
Non-smoking	71.4	15.2	13.4	59.5
Audit-C Score ≥5	72.9	12.12	15.0	52.0
Audit-C Score <5	71.4	16.0	12.6	56.6
Healthy weight status	72.0	16.0	12.0	42.8
Overweight weight status	79.6	10.2	10.2	48.1
Obese weight status	69.7	15.4	14.9	60.8
Comorbidity of diabetes	72.4	12.9	14.7	55.3
Comorbidity of CHD	76.2	12.7	11.1	56.5
Comorbidity of Stroke	50.0	50.0	0.0	85.4

Appendix UFree-text reasons for not being interested in participating in a randomised controlled trial

Table 65: Free-text reasons for not being interested in participating in a randomised controlled trial

Reason
Don't have transport to get to hospital
Hate the taste of coffee
Health not great at present
I do not like coffee
I don't like coffee but would try to if there was no one else!
Only because I hate coffee

Appendix V Misclassification in coffee consumption in the CUPLID survey by subgroup

Table 66: Misclassification in coffee consumption in CUPLID survey by subgroup

Characteristic of participant	Number of participants	Proportion (%) of misclassification of caffeinated coffee consumption using coffee unit measure					Caffeinated instant coffee as % of all coffee
		None	1 cup under	≥2 cups under	1 cup over	≥2 cups over	
Total	231	48.0	26.4	24.3	1.3	0.0	53.1
Male	163	45.7	25.0	29.3	0.0	0.0	51.6
Female	108	51.1	30.0	15.6	3.3	0.0	54.8
Age 18-34	10	55.6	22.2	22.2	0.0	0.0	40.0
Age 35-54	70	37.7	29.5	32.8	0.0	0.0	51.0
Age ≥ 55	190	51.6	26.4	20.1	1.9	0.0	54.1
Liver stiffness <7 kPa	116	49.0	25.5	23.5	2.0	0.0	55.0
Liver stiffness ≥7 to ≤13 kPa	90	46.3	32.9	20.8	0.0	0.0	51.2
Liver stiffness > 13 kPa	65	50.0	20.0	28.0	2.0	0.0	53.4
AUDIT-C score < 5	189	51.0	28.0	20.4	0.6	0.0	55.0
AUDIT-C score ≥ 5	80	40.8	25.4	31.0	2.8	0.0	48.1
>0-3 cups	174	48.0	26.4	24.3	1.3	0.0	48.0
≥4 cups	57	45.7	25.0	29.3	0.0	0.0	68.6

References

1. Williams, R. *et al.* Addressing liver disease in the UK: a blueprint for attaining excellence in health care and reducing premature mortality from lifestyle issues of excess consumption of alcohol, obesity, and viral hepatitis. *Lancet* **384**, 1953–1997 (2014).

2. Hart, C. L., Morrison, D. S., Batty, G. D., Mitchell, R. J. & Davey Smith, G. Effect of body mass index and alcohol consumption on liver disease: analysis of data from two prospective cohort studies. *BMJ* **340**, c1240 (2010).

3. Williams, R. *et al.* Disease burden and costs from excess alcohol consumption, obesity, and viral hepatitis: fourth report of the Lancet Standing Commission on Liver Disease in the UK. *Lancet (London, England)* **391**, 1097–107 (2017).

4. Calzadilla Bertot, L. & Adams, L. A. The Natural Course of Non-Alcoholic Fatty Liver Disease. *Int. J. Mol. Sci.* **17**, (2016).

5. Holman, N., Forouhi, N. G., Goyder, E. & Wild, S. H. The Association of Public Health Laboratories (APHO) diabetes Prevalence Model: estimates of total diabetes prevalence for England, 2010-2030. *Diabet. Med.* **28**, 575–82 (2011).

6. Sattar, N., Forrest, E. & Preiss, D. Non-alcoholic fatty liver disease. *BMJ (Online)* **349**, g4596 (2014).

7. Public Health England. Liver Disease Profiles. (2018). Available at: https://fingertips.phe.org.uk/profile/liver-disease/data#page/6/gid/8000063/pat/6/par/E12000008/ati/102/are/E06000045/iid/90875/age/163/sex/4. (Accessed: 27th May 2019)

8. British Transplantation Society. *Liver Transplantation for Patients with Non-Alcoholic Steato-Hepatitis First Edition*. (2011).

9. Chalasani, N. *et al.* The Diagnosis and Management of Nonalcoholic Fatty Liver Disease: Practice Guidance From the American Association for the Study of Liver Diseases. (2017). doi:10.1002/hep.29367/suppinfo

10. EASL–EASD–EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. *J. Hepatol.* **64**, 1388–1402 (2016).

11. Hagström, H. *et al.* Low to moderate lifetime alcohol consumption is associated with less advanced stages of fibrosis in non-alcoholic fatty liver disease. *Scand. J. Gastroenterol.* **52**, 159–165 (2017).

12. Højland Ipsen, D., Tveden-Nyborg, P. & Lykkesfeldt, J. Normal weight dyslipidemia: Is it all about the liver? *Obesity* **24**, 556–567 (2016).

13. Chalasani, N. *et al.* The Diagnosis and Management of Non-alcoholic Fatty Liver Disease: Practice Guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association. *Am. J. Gastroenterol.* **107**, 811–826 (2012).

14. Than, N. N. & Newsome, P. N. A concise review of non-alcoholic fatty liver disease. *Atherosclerosis* **239**, 192–202 (2015).

15. Francque, S. M., van der Graaff, D. & Kwanten, W. J. Non-alcoholic fatty liver disease and cardiovascular risk: Pathophysiological mechanisms and implications. *J. Hepatol.* **65**, 425–443 (2016).

16. Hossain, N., Kanwar, P. & Mohanty, S. R. A Comprehensive Updated Review of Pharmaceutical and Nonpharmaceutical Treatment for NAFLD. *Gastroenterol. Res. Pract.* **2016**, 1–17 (2016).

17. British Coffee Association. British Coffee Association - Find the coffee facts. (2016). Available at: http://www.britishcoffeeassociation.org/about_coffee/coffee_facts/. (Accessed: 26th February 2017)

18. Ludwig, I. A., Clifford, M. N., Lean, M. E. J., Ashihara, H. & Crozier, A. Coffee: biochemistry and potential impact on health. *Food Funct.* **5**, 1695–717 (2014).

19. Kingston, L. *How to make coffee: The science behind the bean*. (Ivy Press, 2015).

20. International Coffee Organization. International Coffee Organization - The Current State of the Global Coffee Trade | #CoffeeTradeStats. *Website* (2016). Available at: http://www.ico.org/monthly_coffee_trade_stats.asp. (Accessed: 13th February 2017)

21. Casal, S., P P Oliveira, M. B., Alves, M. R. & Ferreira, M. A. Discriminate Analysis of Roasted Coffee Varieties for Trigonelline, Nicotinic Acid, and Caffeine Content. *J. Agric. Food Chem* **48**,

3420–3424 (2000).

22. Gloess, A. N. *et al.* Comparison of nine common coffee extraction methods: instrumental and sensory analysis. *Eur. Food Res. Technol.* **236**, 607–627 (2013).

23. Parras, P., Martínez-Tomé, M., Jiménez, A. M. & Murcia, M. A. Antioxidant capacity of coffees of several origins brewed following three different procedures. *Food Chem.* **102**, 582–92 (2007).

24. George, S. E., Ramalakshmi, K. & Mohan Rao, L. J. A Perception on Health Benefits of Coffee. *Crit. Rev. Food Sci. Nutr.* **48**, 464–486 (2008).

25. Farah, A., De Paulis, T., Trugo, L. C. & Martin, P. R. Effect of Roasting on the Formation of Chlorogenic Acid Lactones in Coffee. *J. Agric. Food Chem.* **53**, 1505–13 (2005).

26. Sunarharum, W. B., Williams, D. J. & Smyth, H. E. Complexity of coffee flavor: A compositional and sensory perspective. *Food Res. Int.* **62**, 315–325 (2014).

27. Cavin, C. *et al.* Cafestol and kahweol, two coffee specific diterpenes with anticarcinogenic activity. *Food Chem. Toxicol.* **40**, 1115–63 (2002).

28. Guertin, K. A. *et al.* Serum biomarkers of habitual coffee consumption may provide insight into the mechanism underlying the association between coffee consumption and colorectal cancer. *Am J Clin Nutr* **101**, 1000–11 (2015).

29. Kumar, P. & Clark, M. Liver, biliary tract and pancreatic diseases. in *Clinical Medicine* 237–241 (Bailliere Tindall Ltd, 1995).

30. Gaw, A., Cowan, R., O'Reilly, D., Stewart, M. & Shepherd, J. Liver Function Tests. in *Clinical Biochemistry* 50–51 (Churchill Livingstone, 1995).

31. Parkes, J. *et al.* Enhanced liver fibrosis test can predict clinical outcomes in patients with chronic liver disease. *Gut* **59**, 1245–51 (2010).

32. Miele, L. *et al.* Enhanced Liver Fibrosis Test as a Reliable Tool for Assessing Fibrosis in Nonalcoholic Fatty Liver Disease in a Clinical Setting. *Int. J. Biol. Markers* **32**, 397–402 (2017).

33. Castera, L. *et al.* EASL-ALEH Clinical Practice Guidelines: Non-invasive tests for evaluation of liver disease severity and prognosis. *J. Hepatol.* **63**, 237–264 (2015).

34. Nilssen, O., Førde, O. H. & Brenn, T. The Tromsø Study. Distribution and population determinants of gamma-glutamyltransferase. *Am. J. Epidemiol.* **132**, 318–26 (1990).

35. Casiglia, E., Spolaore, P., Ginocchio, G. & Ambrosio, G. B. Unexpected effects of coffee consumption on liver enzymes. *Eur. J. Epidemiol.* **9**, 293–7 (1993).

36. Kono, S., Shinchi, K., Imanishi, K., Todoroki, I. & Hatsuse, K. Coffee and serum gamma-glutamyltransferase: a study of self-defense officials in Japan. *Am. J. Epidemiol.* **139**, 723–7 (1994).

37. Tanaka, K. *et al.* Coffee consumption and decreased serum gamma-glutamyltransferase and aminotransferase activities among male alcohol drinkers. *Int. J. Epidemiol.* **27**, 438–43 (1998).

38. Aubin, H. J. *et al.* Joint influence of alcohol, tobacco, and coffee on biological markers of heavy drinking in alcoholics. *Biol. Psychiatry* **44**, 638–43 (1998).

39. Nakanishi, N., Nakamura, K., Suzuki, K. & Tatara, K. Effects of coffee consumption against the development of liver dysfunction: a 4-year follow-up study of middle-aged Japanese male office workers. *Ind. Health* **38**, 99–102 (2000).

40. Honjo, S. *et al.* Coffee drinking and serum gamma-glutamyltransferase: an extended study of Self-Defense Officials of Japan. *Ann. Epidemiol.* **9**, 325–31 (1999).

41. Nakanishi, N., Nakamura, K., Nakajima, K., Suzuki, K. & Tatara, K. Coffee consumption and decreased serum gamma-glutamyltransferase: a study of middle-aged Japanese men. *Eur. J. Epidemiol.* **16**, 419–23 (2000).

42. Honjo, S. *et al.* Coffee consumption and serum aminotransferases in middle-aged Japanese men. *J. Clin. Epidemiol.* **54**, 823–9 (2001).

43. Ruhl, C. E. & Everhart, J. E. Coffee and caffeine consumption reduce the risk of elevated serum alanine aminotransferase activity in the United States. *Gastroenterology* **128**, 24–32 (2005).

44. Ikeda, M. *et al.* Relation of coffee consumption and serum liver enzymes in Japanese men and women with reference to effect modification of alcohol use and body mass index. *Scand. J. Clin. Lab. Invest.* **70**, 171–179 (2010).

45. Jang, E. S. *et al.* Effects of coffee, smoking, and alcohol on liver function tests: a comprehensive cross-sectional study. *BMC Gastroenterol.* **12**, 145 (2012).

46. Danielsson, J., Kangastupa, P., Laatikainen, T., Aalto, M. & Niemela, O. Dose- and Gender-dependent Interactions between Coffee Consumption and Serum GGT Activity in Alcohol Consumers. *Alcohol Alcohol.* **48**, 303–307 (2013).

47. Xiao, Q., Sinha, R., Graubard, B. I. & Freedman, N. D. Inverse associations of total and decaffeinated coffee with liver enzyme levels in National Health and Nutrition Examination Survey 1999-2010. *Hepatology* **60**, 2091–2098 (2014).

48. Weusten-Van der Wouw, M. P. *et al.* Identity of the cholesterol-raising factor from boiled coffee and its effects on liver function enzymes. *J. Lipid Res.* **35**, 721–33 (1994).

49. Urgert, R., Schulz, A. G. & Katan, M. B. Effects of cafestol and kahweol from coffee grounds on serum lipids and serum liver enzymes in humans. *Am. J. Clin. Nutr.* **61**, 149–54 (1995).

50. Boekschoten, M. V, Schouten, E. G. & Katan, M. B. Coffee bean extracts rich and poor in kahweol both give rise to elevation of liver enzymes in healthy volunteers. *Nutr. J.* **3**, 7 (2004).

51. Catalano, D. *et al.* Protective Role of Coffee in Non-alcoholic Fatty Liver Disease (NAFLD). *Dig. Dis. Sci.* **55**, 3200–3206 (2010).

52. Funatsu, K., Yamashita, T. & Nakamura, H. Coffee Consumption is Associated with a Lower Incidence of Fatty Liver in Middle-aged Men. *J. Heal. Sci.* **57**, 406–413 (2011).

53. Dickson, J. C. *et al.* Associations of coffee consumption with markers of liver injury in the insulin resistance atherosclerosis study. *BMC Gastroenterol.* **15**, 88 (2015).

54. Zelber-Sagi, S. *et al.* Coffee consumption and nonalcoholic fatty liver onset: a prospective study in the general population. *Transl. Res.* **165**, 428–436 (2015).

55. Imatoh, T., Kamimura, S. & Miyazaki, M. Coffee but not green tea consumption is associated with prevalence and severity of hepatic steatosis: the impact on leptin level. *Eur. J. Clin. Nutr.* **69**, 1023–1027 (2015).

56. Alferink, L. J. M. *et al.* Coffee and herbal tea consumption is associated with lower liver stiffness in the general population: The Rotterdam study. *J. Hepatol.* **67**, 339–348 (2017).

57. Veronese, N. *et al.* Coffee Intake and Liver Steatosis: A Population Study in a Mediterranean Area. *Nutrients* **10**, (2018).

58. Trovato, F. M., Catalano, D., Musumeci, G. & Trovato, G. M. 4Ps medicine of the fatty liver: the research model of predictive, preventive, personalized and participatory medicine—recommendations for facing obesity, fatty liver and fibrosis epidemics. *EPMA J.* **5**, 21 (2014).

59. Modi, A. A. *et al.* Increased caffeine consumption is associated with reduced hepatic fibrosis.

Hepatology **51**, 201–209 (2010).

60. Molloy, J. W. *et al.* Association of coffee and caffeine consumption with fatty liver disease, nonalcoholic steatohepatitis, and degree of hepatic fibrosis. *Hepatology* **55**, 429–436 (2012).

61. Anty, R. *et al.* Regular coffee but not espresso drinking is protective against fibrosis in a cohort mainly composed of morbidly obese European women with NAFLD undergoing bariatric surgery. *J. Hepatol.* **57**, 1090–1096 (2012).

62. Machado, S. R., Parise, E. R. & de Carvalho, L. Coffee has hepatoprotective benefits in Brazilian patients with chronic hepatitis C even in lower daily consumption than in American and European populations. *Brazilian J. Infect. Dis.* **18**, 170–176 (2014).

63. Bambha, K. *et al.* Coffee consumption in NAFLD patients with lower insulin resistance is associated with lower risk of severe fibrosis. *Liver Int.* **34**, 1250–1258 (2014).

64. Petrick, J. L. *et al.* Coffee Consumption and Risk of Hepatocellular Carcinoma and Intrahepatic Cholangiocarcinoma by Sex: The Liver Cancer Pooling Project. *Cancer Epidemiol. Biomarkers Prev.* **24**, 1398–1406 (2015).

65. Liu, F. *et al.* Coffee consumption decreases risks for hepatic Fibrosis and Cirrhosis: A Meta-Analysis. *PLoS One* **10**, e0142457 (2015).

66. Shen, H. *et al.* Association between caffeine consumption and nonalcoholic fatty liver disease: a systemic review and meta-analysis. *Therap. Adv. Gastroenterol.* **9**, 113–120 (2016).

67. Klatsky, A. L. & Armstrong, M. A. Alcohol, smoking, coffee, and cirrhosis. *Am. J. Epidemiol.* **136**, 1248–57 (1992).

68. Corrao, G. *et al.* The effect of drinking coffee and smoking cigarettes on the risk of cirrhosis associated with alcohol consumption. A case-control study. Provincial Group for the Study of Chronic Liver Disease. *Eur. J. Epidemiol.* **10**, 657–64 (1994).

69. Corrao, G. *et al.* Coffee, caffeine, and the risk of liver cirrhosis. *Ann. Epidemiol.* **11**, 458–65 (2001).

70. Gallus, S., Tavani, A., Negri, E. & La Vecchia, C. Does coffee protect against liver cirrhosis? *Ann. Epidemiol.* **12**, 202–5 (2002).

71. Tverdal, A. & Skurtveit, S. Coffee intake and mortality from liver cirrhosis. *Ann. Epidemiol.* **13**,

419–23 (2003).

72. Klatsky, A. L., Morton, C., Udaltsova, N. & Friedman, G. D. Coffee, Cirrhosis, and Transaminase Enzymes. *Arch. Intern. Med.* **166**, 1190 (2006).

73. Stroffolini, T. *et al.* Interaction of alcohol intake and cofactors on the risk of cirrhosis. *Liver Int.* **30**, 867–870 (2009).

74. Walton, H., Masterton, G. & Hayes, P. An epidemiological study of the association of coffee with chronic liver disease. *Scott. Med. J.* **58**, 217–222 (2013).

75. Goh, G. B.-B., Chow, W.-C., Wang, R., Yuan, J.-M. & Koh, W.-P. Coffee, alcohol and other beverages in relation to cirrhosis mortality: The Singapore Chinese Health Study. *Hepatology* **60**, 661–669 (2014).

76. Setiawan, V. W. *et al.* Coffee Drinking and Alcoholic and Nonalcoholic Fatty Liver Diseases and Viral Hepatitis in the Multiethnic Cohort. *Clin. Gastroenterol. Hepatol.* **15**, 1305–1307 (2017).

77. Kennedy, O. J. *et al.* Systematic review with meta-analysis: coffee consumption and the risk of cirrhosis. *Aliment. Pharmacol. Ther.* **43**, 562–574 (2016).

78. Gallus, S. *et al.* Does coffee protect against hepatocellular carcinoma? *Br. J. Cancer* **87**, 956–959 (2002).

79. Inoue, M., Yoshimi, I., Sobue, T., Tsugane, S. & JPHC Study Group. Influence of Coffee Drinking on Subsequent Risk of Hepatocellular Carcinoma: A Prospective Study in Japan. *JNCI J. Natl. Cancer Inst.* **97**, 293–300 (2005).

80. Shimazu, T. *et al.* Coffee consumption and the risk of primary liver cancer: Pooled analysis of two prospective studies in Japan. *Int. J. Cancer* **116**, 150–154 (2005).

81. Gelatti, U. *et al.* Coffee consumption reduces the risk of hepatocellular carcinoma independently of its aetiology: a case-control study. *J. Hepatol.* **42**, 528–34 (2005).

82. Kurozawa, Y. *et al.* Coffee and risk of death from hepatocellular carcinoma in a large cohort study in Japan. *Br. J. Cancer* **93**, 607–610 (2005).

83. Montella, M. *et al.* Coffee and tea consumption and risk of hepatocellular carcinoma in Italy. *Int. J. Cancer* **120**, 1555–1559 (2007).

84. Tanaka, K. *et al.* Inverse association between coffee drinking and the risk of hepatocellular

carcinoma: a case-control study in Japan. *Cancer Sci.* **98**, 214–218 (2007).

85. Wakai, K. *et al.* Liver cancer risk, coffee, and hepatitis C virus infection: a nested case–control study in Japan. *Br. J. Cancer* **97**, 426–428 (2007).

86. Hu, G. *et al.* Joint effects of coffee consumption and serum gamma-glutamyltransferase on the risk of liver cancer. *Hepatology* **48**, 129–136 (2008).

87. Inoue, M. *et al.* Effect of Coffee and Green Tea Consumption on the Risk of Liver Cancer: Cohort Analysis by Hepatitis Virus Infection Status. *Cancer Epidemiol. Biomarkers Prev.* **18**, 1746–1753 (2009).

88. Johnson, S. *et al.* Coffee consumption and reduced risk of hepatocellular carcinoma: findings from the Singapore Chinese Health Study. *Cancer Causes Control* **22**, 503–510 (2011).

89. Lai, G. Y. *et al.* The association of coffee intake with liver cancer incidence and chronic liver disease mortality in male smokers. *Br. J. Cancer* **109**, 1344–1351 (2013).

90. Jang, E. S. *et al.* The effect of coffee consumption on the development of hepatocellular carcinoma in hepatitis B virus endemic area. *Liver Int.* **33**, 1092–9 (2013).

91. Bamia, C. *et al.* Coffee, tea and decaffeinated coffee in relation to hepatocellular carcinoma in a European population: Multicentre, prospective cohort study. *Int. J. Cancer* **136**, 1899–1908 (2015).

92. Setiawan, V. W. *et al.* Association of coffee intake with reduced incidence of liver cancer and death from chronic liver disease in the US multiethnic cohort. *Gastroenterology* **148**, 118–25; quiz e15 (2015).

93. Aleksandrova, K. *et al.* The association of coffee intake with liver cancer risk is mediated by biomarkers of inflammation and hepatocellular injury: data from the European Prospective Investigation into Cancer and Nutrition. *Am. J. Clin. Nutr.* **102**, 1498–1508 (2015).

94. Cardin, R. *et al.* Effects of coffee consumption in chronic hepatitis C: A randomized controlled trial. *Dig. Liver Dis.* **45**, 499–504 (2013).

95. Bravi, F. *et al.* Coffee drinking and hepatocellular carcinoma risk: A meta-analysis. *Hepatology* **46**, 430–435 (2007).

96. Larsson, S. C. & Wolk, A. Coffee Consumption and Risk of Liver Cancer: A Meta-Analysis.

Gastroenterology **132**, 1740–1745 (2007).

97. Bravi, F., Bosetti, C., Tavani, A., Gallus, S. & La Vecchia, C. Coffee Reduces Risk for Hepatocellular Carcinoma: An Updated Meta-analysis. *Clin. Gastroenterol. Hepatol.* **11**, 1413-1421.e1 (2013).

98. Sang, L.-X., Chang, B., Li, X.-H. & Jiang, M. Consumption of coffee associated with reduced risk of liver cancer: a meta-analysis. *BMC Gastroenterol.* **13**, 34 (2013).

99. Jaruvongvanich, V., Sanguankeo, A., Klomjit, N. & Upala, S. Effects of caffeine consumption in patients with chronic hepatitis C: A systematic review and meta-analysis. *Clin. Res. Hepatol. Gastroenterol.* (2016). doi:10.1016/j.clinre.2016.05.012

100. Bravi, F., Tavani, A., Bosetti, C., Boffetta, P. & La Vecchia, C. Coffee and the risk of hepatocellular carcinoma and chronic liver disease. *Eur. J. Cancer Prev.* 1 (2016). doi:10.1097/CEJ.0000000000000252

101. Bai, K., Cai, Q., Jiang, Y. & Lv, L. Coffee consumption and risk of hepatocellular carcinoma: a meta-analysis of eleven epidemiological studies. *Onco. Targets. Ther.* **9**, 4369–75 (2016).

102. Yu, C. *et al.* An updated dose-response meta-analysis of coffee consumption and liver cancer risk. *Sci. Rep.* **6**, 37488 (2016).

103. Kennedy, O. J. *et al.* Coffee, including caffeinated and decaffeinated coffee, and the risk of hepatocellular carcinoma: a systematic review and dose–response meta-analysis. *BMJ Open* **7**, e013739 (2017).

104. Godos, J. *et al.* Coffee Consumption and Risk of Biliary Tract Cancers and Liver Cancer: A Dose–Response Meta-Analysis of Prospective Cohort Studies. *Nutrients* **9**, 950 (2017).

105. Wijarnpreecha, K., Thongprayoon, C., Ungprasert, P., K., W. & C., T. Coffee consumption and risk of nonalcoholic fatty liver disease: A systematic review and meta-analysis. *Eur. J. Gastroenterol. Hepatol.* **29**, e8–e12 (2017).

106. Chen, Y.-P. *et al.* A systematic review and a dose–response meta-analysis of coffee dose and nonalcoholic fatty liver disease. *Clin. Nutr.* (2018). doi:10.1016/j.clnu.2018.11.030

107. Younossi, Z. M. *et al.* Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. *Hepatology* **64**, 73–84 (2016).

108. Bessone, F., Razori, M. V. & Roma, M. G. Molecular pathways of nonalcoholic fatty liver disease development and progression. *Cell. Mol. Life Sci.* (2018). doi:10.1007/s00018-018-2947-0

109. Ipsen, D. H., Lykkesfeldt, J. & Tveden-Nyborg, P. Molecular mechanisms of hepatic lipid accumulation in non-alcoholic fatty liver disease. *Cell. Mol. Life Sci.* **75**, 3313 (2018).

110. Lucas, C., Lucas, G., Lucas, N., Krzowska-Firych, J. & Tomasiewicz, K. A systematic review of the present and future of non-alcoholic fatty liver disease. *Clin. Exp. Hepatol.* **4**, 165–174 (2018).

111. Salomone, F., Galvano, F. & Li Volti, G. Molecular Bases Underlying the Hepatoprotective Effects of Coffee. *Nutrients* **9**, 85 (2017).

112. Alferink, L., Kiefte-de Jong, J. & Darwish Murad, S. Potential Mechanisms Underlying the Role of Coffee in Liver Health. *Semin. Liver Dis.* **38**, 193–214 (2018).

113. Devasagayam, T. P., Kamat, J. P., Mohan, H. & Kesavan, P. C. Caffeine as an antioxidant: inhibition of lipid peroxidation induced by reactive oxygen species. *Biochim. Biophys. Acta* **1282**, 63–70 (1996).

114. Gordillo-Bastidas, D. *et al.* Nrf2 and Snail-1 in the prevention of experimental liver fibrosis by caffeine. *World J. Gastroenterol.* **19**, 9020 (2013).

115. Shim, S. G. *et al.* Caffeine attenuates liver fibrosis via defective adhesion of hepatic stellate cells in cirrhotic model. *J. Gastroenterol. Hepatol.* **28**, 1877–1884 (2013).

116. Tao, K.-S. *et al.* The multifaceted mechanisms for coffee's anti-tumorigenic effect on liver. *Med. Hypotheses* **71**, 730–736 (2008).

117. Kubo Shlonsky, A., Klatsky, A. L. & Armstrong, M. A. Traits of persons who drink decaffeinated coffee. *Ann. Epidemiol.* **13**, 273–9 (2003).

118. Aromataris, E. *et al.* Summarizing systematic reviews: methodological development, conduct and reporting of an umbrella review approach. *Int. J. Evidence-Based Healthc. Joanna Briggs Inst. Int J Evid Based Heal.* **13**, 132–140 (2015).

119. SIGN. Scottish Intercollegiate Guidelines Network Search Filters. (2015). Available at: http://www.sign.ac.uk/methodology/filters.html. (Accessed: 14th December 2016)

120. Shea, B. J. *et al.* AMSTAR is a reliable and valid measurement tool to assess the methodological quality of systematic reviews. *J. Clin. Epidemiol.* **62**, 1013–1020 (2009).

121. Pieper, D., Mathes, T. & Eikermann, M. Can AMSTAR also be applied to systematic reviews of non-randomized studies? *BMC Res. Notes* **7**, 1–6 (2014).

122. Guyatt, G. *et al.* GRADE guidelines: 1. Introduction—GRADE evidence profiles and summary of findings tables. *J. Clin. Epidemiol.* **64**, 383–394 (2011).

123. DerSimonian, R. & Laird, N. Meta-analysis in clinical trials revisited. *Contemp. Clin. Trials* **45**, 139–45 (2015).

124. Sterne, J. A. ., Gavaghan, D. & Egger, M. Publication and related bias in meta-analysis. *J. Clin. Epidemiol.* **53**, 1119–1129 (2000).

125. Altman, D. G. & Bland, J. M. Interaction revisited: the difference between two estimates. *BMJ* **326**, 219 (2003).

126. Crippa, A. Personal communication with Alessio Crippa. (2017).

127. Ding, M., Bhupathiraju, S. N., Satija, A., van Dam, R. M. & Hu, F. B. Long-Term Coffee Consumption and Risk of Cardiovascular Disease: A Systematic Review and a Dose-Response Meta-Analysis of Prospective Cohort Studies. *Circulation* **129**, 643–659 (2014).

128. Gan, Y. *et al.* Association of coffee consumption with risk of colorectal cancer: a meta-analysis of prospective cohort studies. *Oncotarget* **8**, 18699–18711 (2017).

129. Ding, M., Bhupathiraju, S. N., Chen, M., van Dam, R. M. & Hu, F. B. Caffeinated and Decaffeinated Coffee Consumption and Risk of Type 2 Diabetes: A Systematic Review and a Dose-Response Meta-analysis. *Diabetes Care* **37**, 569–586 (2014).

130. Qi, H. & Li, S. Dose-response meta-analysis on coffee, tea and caffeine consumption with risk of Parkinson's disease. *Geriatr. Gerontol. Int.* **14**, 430–439 (2014).

131. Li, J. *et al.* A meta-analysis of risk of pregnancy loss and caffeine and coffee consumption during pregnancy. *Int. J. Gynecol. Obstet.* **130**, 116–122 (2015).

132. Mostofsky, E., Rice, M. S., Levitan, E. B. & Mittleman, M. A. Habitual coffee consumption and risk of heart failure: a dose-response meta-analysis. *Circ. Heart Fail.* **5**, 401–5 (2012).

133. Zhang, Y.-P. *et al.* Systematic review with meta-analysis: Coffee consumption and the risk of gallstone disease. *Aliment. Pharmacol. Ther.* **42**, 637–648 (2015).

134. Shang, F., Li, X., Jiang, X., F., S. & X., L. Coffee consumption and risk of the metabolic syndrome:

A meta-analysis. *Diabetes Metab.* **42**, 80–87 (2016).

135. Je, Y. & Giovannucci, E. Coffee consumption and total mortality: a meta-analysis of twenty prospective cohort studies. *Br. J. Nutr.* **111**, 1162–1173 (2014).

136. Thomopoulos, T. P. *et al.* Maternal and childhood consumption of coffee, tea and cola beverages in association with childhood leukemia: a meta-analysis. *Cancer Epidemiol.* **39**, 1047–1059 (2015).

137. Xie, Y. *et al.* Coffee consumption and the risk of lung cancer: an updated meta-analysis of epidemiological studies. *Eur. J. Clin. Nutr.* **70**, 199–206 (2016).

138. Lee, Y. H., Bae, S.-C. & Song, G. G. Coffee or tea consumption and the risk of rheumatoid arthritis: a meta-analysis. *Clin. Rheumatol.* **33**, 1575–1583 (2014).

139. Lee, Y. H., Bae, S.-C. & Song, G. G. Erratum to: Coffee or tea consumption and the risk of rheumatoid arthritis: a meta-analysis. *Clin. Rheumatol.* **34**, 403–405 (2015).

140. Rhee, J. *et al.* Maternal Caffeine Consumption during Pregnancy and Risk of Low Birth Weight: A Dose-Response Meta-Analysis of Observational Studies. *PLoS One* **10**, e0132334 (2015).

141. Wang, A. *et al.* Coffee and cancer risk: A meta-analysis of prospective observational studies. *Sci. Rep.* **6**, 33711 (2016).

142. Ouyang, Z., Wang, Z. & Jin, J. Association between tea and coffee consumption and risk of laryngeal cancer: a meta-analysis. *Int. J. Clin. Exp. Med.* **7**, 5192–5200 (2014).

143. Maslova, E., Bhattacharya, S., Lin, S.-W. & Michels, K. B. Caffeine consumption during pregnancy and risk of preterm birth: a meta-analysis. *Am. J. Clin. Nutr.* **92**, 1120–1132 (2010).

144. Browne, M. L. Maternal exposure to caffeine and risk of congenital anomalies: a systematic review. *Epidemiology* **17**, 324–331 (2006).

145. Li, S., Dai, Z., Wu, Q., S., L. & Z., D. Effect of coffee intake on hip fracture: a meta-analysis of prospective cohort studies. *Nutr. J.* **14**, 38 (2015).

146. Zhang, Z. *et al.* Habitual coffee consumption and risk of hypertension: a systematic review and meta-analysis of prospective observational studies. *Am. J. Clin. Nutr.* **93**, 1212–1219 (2011).

147. Grosso, G. *et al.* Coffee consumption and risk of all-cause, cardiovascular, and cancer mortality in smokers and non-smokers: a dose-response meta-analysis. *Eur. J. Epidemiol.* **31**, 1191–1205

(2016).

148. Kim, J. *et al.* Association between coffee intake and gastroesophageal reflux disease: a meta-analysis. *Dis. Esophagus* **27**, 311–317 (2014).

149. Han, M. A. & Kim, J. H. Coffee Consumption and the Risk of Thyroid Cancer: A Systematic Review and Meta-Analysis. *Int. J. Environ. Res. Public Health* **14**, (2017).

150. Lee, D. R. *et al.* Coffee consumption and risk of fractures: a systematic review and dose-response meta-analysis. *Bone* **63**, 20–28 (2014).

151. Nie, K., Xing, Z., Huang, W., Wang, W. & Liu, W. Coffee intake and risk of pancreatic cancer: an updated meta-analysis of prospective studies. *Minerva Med.* **107**, 270–278 (2016).

152. Malerba, S. *et al.* A meta-analysis of coffee and tea consumption and the risk of glioma in adults. *Cancer Causes Control* **24**, 267–276 (2013).

153. Liu, Q.-P. *et al.* Habitual coffee consumption and risk of cognitive decline/dementia: A systematic review and meta-analysis of prospective cohort studies. *Nutrition* **32**, 628–636 (2016).

154. Larsson, S. C. *et al.* Coffee consumption is not associated with increased risk of atrial fibrillation: Results from two prospective cohorts and a meta-analysis. *BMC Med.* **13**, 207 (2015).

155. Lippi, G., Mattiuzzi, C. & Franchini, M. Venous thromboembolism and coffee: critical review and meta-analysis. *Ann. Transl. Med.* **3**, 152 (2015).

156. Yu, X., Bao, Z., Zou, J. & Dong, J. Coffee consumption and risk of cancers: a meta-analysis of cohort studies. *BMC Cancer* **11**, 96 (2011).

157. Caini, S. *et al.* Coffee, tea and caffeine intake and the risk of non-melanoma skin cancer: a review of the literature and meta-analysis. *European Journal of Nutrition* **56**, 1 (2017).

158. Zhou, Q., Luo, M.-L., Li, H., Li, M. & Zhou, J.-G. Coffee consumption and risk of endometrial cancer: a dose-response meta-analysis of prospective cohort studies. *Sci. Rep.* **5**, 13410 (2015).

159. Yew, Y. W., Lai, Y. C., Schwartz, R. A., Y.W., Y. & Y.C., L. Coffee Consumption and Melanoma: A Systematic Review and Meta-Analysis of Observational Studies. *Am. J. Clin. Dermatol.* **17**, 113–123 (2016).

160. Liu, F. *et al.* Coffee Consumption Decreases Risks for Hepatic Fibrosis and Cirrhosis: A Meta-Analysis. *PLoS One* **10**, e0142457 (2015).

161. Wang, S. *et al.* A meta-analysis of coffee intake and risk of urolithiasis. *Urol. Int.* **93**, 220–228 (2014).

162. Brown, O. I., Allgar, V. & Wong, K. Y.-K. Coffee reduces the risk of death after acute myocardial infarction. *Coron. Artery Dis.* **27**, 566–572 (2016).

163. Park, K. Y. *et al.* Effects of coffee consumption on serum uric acid: Systematic review and meta-analysis. *Semin. Arthritis Rheum.* **45**, 580–586 (2016).

164. Bravi, F., Tavani, A., Bosetti, C., Boffetta, P. & La Vecchia, C. Coffee and the risk of hepatocellular carcinoma and chronic liver disease: a systematic review and meta-analysis of prospective studies. *Eur. J. Cancer Prev.* (2016). doi:10.1097/CEJ.0000000000000252

165. Yan, K. *et al.* The associations between maternal factors during pregnancy and the risk of childhood acute lymphoblastic leukemia: A meta-analysis. *Pediatr. Blood Cancer* **62**, 1162–1170 (2015).

166. Yan, K. *et al.* Corrigendum: The Associations Between Maternal Factors During Pregnancy and the Risk of Childhood Acute Lymphoblastic Leukemia: A Meta-Analysis. *Pediatric Blood & Cancer* **63**, 953–954 (2016).

167. Han, T., Li, J., Wang, L. & Xu, H. Coffee and the Risk of Lymphoma: A Meta-analysis Article. *Iran. J. Public Health* **45**, 1126–1135 (2016).

168. Galarraga, V. & Boffetta, P. Coffee Drinking and Risk of Lung Cancer—A Meta-Analysis. *Cancer Epidemiol. Prev. Biomarkers* **25**, (2016).

169. Zeegers, M. P. *et al.* Are coffee and tea consumption associated with urinary tract cancer risk? A systematic review and meta-analysis. *Int. J. Epidemiol.* **30**, 353–362 (2001).

170. Chiaffarino, F. *et al.* Coffee and caffeine intake and risk of endometriosis: a meta-analysis. *Eur. J. Nutr.* **53**, 1573–1579 (2014).

171. Steffen, M. *et al.* The effect of coffee consumption on blood pressure and the development of hypertension: A systematic review and meta-analysis. *J. Hypertens.* **30**, 2245–2254 (2012).

172. Fang, X. *et al.* Landscape of dietary factors associated with risk of gastric cancer: A systematic review and dose-response meta-analysis of prospective cohort studies. *Eur. J. Cancer* **51**, 2820–2832 (2015).

173. Galeone, C., Turati, F., La Vecchia, C. & Tavani, A. Coffee consumption and risk of colorectal cancer: a meta-analysis of case–control studies. *Cancer Causes Control* **21**, 1949–1959 (2010).

174. Mack, W. J. *et al.* A pooled analysis of case-control studies of thyroid cancer: cigarette smoking and consumption of alcohol, coffee, and tea. *Cancer Causes Control* **14**, 773–785 (2003).

175. Zhang, R., Wang, Y., Song, B., Jørgensen, H. & Xu, Y. Coffee consumption and risk of stroke: a meta-analysis of cohort studies. *Open Med.* **7**, 310–316 (2012).

176. Cao, S. *et al.* Coffee consumption and risk of prostate cancer: a meta-analysis of prospective cohort studies. *Carcinogenesis* **35**, 256–261 (2014).

177. Li, Z.-X. *et al.* Maternal Coffee Consumption During Pregnancy and Neural Tube Defects in Offspring: A Meta-Analysis. *Fetal Pediatr. Pathol.* **35**, 1–9 (2016).

178. Bravi, F. *et al.* Coffee drinking and endometrial cancer risk: a metaanalysis of observational studies. *Am. J. Obstet. Gynecol.* **200**, 130–135 (2009).

179. Sun, S., Liu, D., Jiao, Z., S., S. & D., L. Coffee and caffeine intake and risk of urinary incontinence: a meta-analysis of observational studies. *BMC Urol.* **16**, 1–7 (2016).

180. Barranco Quintana, J. L., Allam, M. F., Serrano Del Castillo, A. & Fernandez-Crehuet Navajas, R. Alzheimer's disease and coffee: a quantitative review. *Neurol. Res.* **29**, 91–95 (2007).

181. Wijarnpreecha, K. *et al.* Association of coffee consumption and chronic kidney disease: A meta-analysis. *Int. J. Clin. Pract.* **71**, e12919 (2017).

182. Noyce, A. J. *et al.* Meta-analysis of early nonmotor features and risk factors for Parkinson disease. *Ann. Neurol.* **72**, 893–901 (2012).

183. Chen, L.-W. *et al.* Maternal caffeine intake during pregnancy is associated with risk of low birth weight: a systematic review and dose-response meta-analysis. *BMC Med.* **12**, 174 (2014).

184. Wu, W. *et al.* Coffee consumption and bladder cancer: a meta-analysis of observational studies. *Sci. Rep.* **5**, 9051 (2015).

185. Liu, H. *et al.* Coffee consumption and risk of fractures: a meta-analysis. *Arch. Med. Sci.* **8**, 776–783 (2012).

186. Zeng, S.-B. *et al.* Long-Term Coffee Consumption and Risk of Gastric Cancer: A PRISMA-Compliant Dose-Response Meta-Analysis of Prospective Cohort Studies. *Med. (United States)* **94**,

e1640 (2015).

187. Braem, M. G. M. *et al.* Coffee and tea consumption and the risk of ovarian cancer: A prospective cohort study and updated meta-analysis. *Am. J. Clin. Nutr.* **95**, 1172–1181 (2012).

188. Malerba, S. *et al.* A meta-analysis of prospective studies of coffee consumption and mortality for all causes, cancers and cardiovascular diseases. *Eur. J. Epidemiol.* **28**, 527–539 (2013).

189. Zheng, J.-S. *et al.* Effects of green tea, black tea, and coffee consumption on the risk of esophageal cancer: a systematic review and meta-analysis of observational studies. *Nutr. Cancer* **65**, 1–16 (2013).

190. Li, X.-L. & Xu, J.-H. Coffee consumption and hip fracture risk: a meta-analysis. *J. Nutr. Sci.* **2**, e23 (2013).

191. Li, X. J. *et al.* Coffee Consumption and Risk of Breast Cancer: An Up-To-Date Meta-Analysis. *PLoS One* **8**, e52681 (2013).

192. Ran, H.-Q., Wang, J.-Z. & Sun, C.-Q. Coffee Consumption and Pancreatic Cancer Risk: An Update Meta-analysis of Cohort Studies. *Pakistan J. Med. Sci.* **32**, 253–9 (2016).

193. Wang, J., Li, X. & Zhang, D. Coffee consumption and the risk of cutaneous melanoma: a meta-analysis. *Eur. J. Nutr.* (2015). doi:10.1007/s00394-015-1139-z

194. Huang, T. *et al.* Coffee consumption and urologic cancer risk: a meta-analysis of cohort studies. *Int. Urol. Nephrol.* **46**, 1481–1493 (2014).

195. Jiang, X., Zhang, D., Jiang, W., X., J. & D., Z. Coffee and caffeine intake and incidence of type 2 diabetes mellitus: a meta-analysis of prospective studies. *Eur. J. Nutr.* **53**, 25–38 (2014).

196. Wang, L., Shen, X., Wu, Y. & Zhang, D. Coffee and caffeine consumption and depression: A meta-analysis of observational studies. *Aust. N. Z. J. Psychiatry* (2015). doi:10.1177/0004867415603131

197. Hernán, M. A., Takkouche, B., Caamaño-Isorna, F. & Gestal-Otero, J. J. A meta-analysis of coffee drinking, cigarette smoking, and the risk of Parkinson's disease. *Ann. Neurol.* **52**, 276–284 (2002).

198. Kennedy, O. J. *et al.* Systematic review with meta-analysis: Coffee consumption and the risk of cirrhosis. *Aliment. Pharmacol. Ther.* **43**, 562–574 (2016).

199. Sofi, F. *et al.* Coffee consumption and risk of coronary heart disease: a meta-analysis. *Nutr.*

Metab. Cardiovasc. Dis. **17**, 209–223 (2007).

200. Jiang, W., Wu, Y. & Jiang, X. Coffee and caffeine intake and breast cancer risk: an updated dose-response meta-analysis of 37 published studies. *Gynecol. Oncol.* **129**, 620–629 (2013).

201. Liu, J., Shen, B., Shi, M. & Cai, J. Higher Caffeinated Coffee Intake Is Associated with Reduced Malignant Melanoma Risk: A Meta-Analysis Study. *PLoS One* **11**, e0147056 (2016).

202. Tang, N. *et al.* Coffee consumption and risk of lung cancer: A meta-analysis. *Lung Cancer* **67**, 17–22 (2010).

203. Cai, L., Ma, D., Zhang, Y., Liu, Z. & Wang, P. The effect of coffee consumption on serum lipids: a meta-analysis of randomized controlled trials. *Eur. J. Clin. Nutr.* **66**, 872–877 (2012).

204. Jahanfar, S. & Jaafar, S. H. Effects of restricted caffeine intake by mother on fetal, neonatal and pregnancy outcomes. in *Cochrane Database of Systematic Reviews* (ed. Jahanfar, S.) (John Wiley & Sons, Ltd, 2015). doi:10.1002/14651858.CD006965.pub4

205. Larsson, S. C., Drca, N., Jensen-Urstad, M. & Wolk, A. Coffee consumption is not associated with increased risk of atrial fibrillation: results from two prospective cohorts and a meta-analysis. *BMC Med.* **13**, 207 (2015).

206. Heart UK. Cholesterol and triglyceride level conversion. Available at: https://heartuk.org.uk/files/uploads/documents/huk_fs_mfsP_cholestrigly_leverlsconversion.pdf. (Accessed: 3rd August 2017)

207. Liu, H. *et al.* Coffee Consumption and Prostate Cancer Risk: A Meta-Analysis of Cohort Studies. *Nutr. Cancer* **67**, 392–400 (2015).

208. Bravi, F. *et al.* Coffee and the risk of hepatocellular carcinoma and chronic liver disease: a systematic review and meta-analysis of prospective studies. *Eur. J. Cancer Prev.* (2016). doi:10.1097/CEJ.0000000000000252

209. Grosso, G., Micek, A., Castellano, S., Pajak, A. & Galvano, F. Coffee, tea, caffeine and risk of depression: A systematic review and dose-response meta-analysis of observational studies. *Mol. Nutr. Food Res.* **60**, 223–234 (2016).

210. Yew, Y. W., Lai, Y. C. & Schwartz, R. A. Coffee Consumption and Melanoma: A Systematic Review and Meta-Analysis of Observational Studies. *Am. J. Clin. Dermatol.* (2015). doi:10.1007/s40257-015-0165-1

211. Grosso, L. M. & Bracken, M. B. Caffeine Metabolism, Genetics, and Perinatal Outcomes: A Review of Exposure Assessment Considerations during Pregnancy. *Ann. Epidemiol.* **15**, 460–466 (2005).

212. Wierzejska, R., Jarosz, M., Siuba, M. & Sawicki, W. Comparison of maternal and fetal blood levels of caffeine and its metabolite. A pilot study. *Ginekol. Pol.* **85**, 500–3 (2014).

213. O'Hara, K., Wright, I. M. R., Schneider, J. J., Jones, A. L. & Martin, J. H. Pharmacokinetics in neonatal prescribing: evidence base, paradigms and the future. *Br. J. Clin. Pharmacol.* **80**, 1281–1288 (2015).

214. Heaney, R. Effects of caffeine on bone and the calcium economy. *Food Chem. Toxicol.* **40**, 1263–1270 (2002).

215. Hallstrom, H. *et al.* Long-term Coffee Consumption in Relation to Fracture Risk and Bone Mineral Density in Women. *Am. J. Epidemiol.* **178**, 898–909 (2013).

216. Wikoff, D. *et al.* Systematic review of the potential adverse effects of caffeine consumption in healthy adults, pregnant women, adolescents, and children. *Food Chem. Toxicol.* (2017). doi:10.1016/j.fct.2017.04.002

217. Barrett-Connor, E., Chang, J. C. & Edelstein, S. L. Coffee-Associated Osteoporosis Offset by Daily Milk Consumption. *JAMA* **271**, 280 (1994).

218. Sisti, J. S. *et al.* Caffeine, coffee, and tea intake and urinary estrogens and estrogen metabolites in premenopausal women. *Cancer Epidemiol. Biomarkers Prev.* **24**, 1174–83 (2015).

219. Kotsopoulos, J., Eliassen, A. H., Missmer, S. A., Hankinson, S. E. & Tworoger, S. S. Relationship between caffeine intake and plasma sex hormone concentrations in premenopausal and postmenopausal women. *Cancer* **115**, 2765–74 (2009).

220. Goderie-Plomp, H. W. *et al.* Endogenous Sex Hormones, Sex Hormone-Binding Globulin, and the Risk of Incident Vertebral Fractures in Elderly Men and Women: The Rotterdam Study. *J. Clin. Endocrinol. Metab.* **89**, 3261–3269 (2004).

221. Bjørnerem, A. *et al.* A prospective study of sex steroids, sex hormone-binding globulin, and non-vertebral fractures in women and men: the Tromso Study. *Eur. J. Endocrinol.* **157**, 119–25 (2007).

222. Wedick, N. M. *et al.* The effects of caffeinated and decaffeinated coffee on sex hormone-binding globulin and endogenous sex hormone levels: a randomized controlled trial. *Nutr. J.* **11**, 86

(2012).

223. Hallström, H., Wolk, A., Glynn, A. & Michaëlsson, K. Coffee, tea and caffeine consumption in relation to osteoporotic fracture risk in a cohort of Swedish women. *Osteoporos. Int.* **17**, 1055–1064 (2006).

224. Treur, J. L. *et al.* Associations between smoking and caffeine consumption in two European cohorts. *Addiction* **111**, 1059–68 (2016).

225. Urgert, R. & Katan, M. B. The cholesterol-raising factor from coffee beans. *J. R. Soc. Med. J R Soc Med* **8989**, 618–623 (1996).

226. Urgert, R. & Katan, M. B. The cholesterol-raising factor from coffee beans. *J. R. Soc. Med.* **89**, 618–23 (1996).

227. Svilaas, A. *et al.* Human Nutrition and Metabolism Intakes of Antioxidants in Coffee, Wine, and Vegetables Are Correlated with Plasma Carotenoids in Humans 1. *J. Nutr* **134**, 562–567 (2004).

228. Kamiyama, M., Moon, J.-K., Jang, H. W. & Shibamoto, T. Role of Degradation Products of Chlorogenic Acid in the Antioxidant Activity of Roasted Coffee. *J. Agric. Food Chem.* **63**, 1996–2005 (2015).

229. Ramalakshmi, K. & Raghavan, B. Caffeine in Coffee: Its Removal. Why and How? *Crit. Rev. Food Sci. Nutr.* **39**, 441–456 (1999).

230. Woodward, M. *Epidemiology : study design and data analysis*. (Taylor & Francis, 2014).

231. Hartung, J. & Knapp, G. A refined method for the meta-analysis of controlled clinical trials with binary outcome. *Stat. Med.* **20**, 3875–3889 (2001).

232. Greenland, S. & Longnecker, M. P. Methods for Trend Estimation from Summarized Dose-Response Data, with Applications to Meta-Analysis. *Am. J. Epidemiol.* **135**, 1301–1309 (1992).

233. Peters, J. L., Sutton, A. J., Jones, D. R., Abrams, K. R. & Rushton, L. Comparison of Two Methods to Detect Publication Bias in Meta-analysis. *JAMA* **295**, 676 (2006).

234. Ioannidis, J. P. & Trikalinos, T. A. An exploratory test for an excess of significant findings. *Clin. Trials* **4**, 245–253 (2007).

235. Cochrane. Testing for excess of studies with significant results. *Cochrane handbook fo systematic reviews of interventions* (2011). Available at:

http://handbook.cochrane.org/chapter_10/10_4_4_6_testing_for_excess_of_studies_with_significant_results.htm. (Accessed: 20th April 2017)

236. Gunter, M. J. *et al.* Coffee Drinking and Mortality in 10 European Countries: A Multinational Cohort Study. *Ann. Intern. Med.* (2017). doi:10.7326/M16-2945

237. Park, S.-Y. *et al.* Association of Coffee Consumption With Total and Cause-Specific Mortality Among Nonwhite Populations. *Ann. Intern. Med.* **26**, 20–9 (2017).

238. Nordestgaard, A. T., Thomsen, M. & Nordestgaard, B. G. Coffee intake and risk of obesity, metabolic syndrome and type 2 diabetes: a Mendelian randomization study. *Int. J. Epidemiol.* **44**, 551–565 (2015).

239. Nordestgaard, A. T. & Nordestgaard, B. G. Coffee intake, cardiovascular disease and all-cause mortality: observational and Mendelian randomization analyses in 95 000-223 000 individuals. *Int. J. Epidemiol.* **45**, 1938–1952 (2016).

240. Palatini, P. *et al.* CYP1A2 genotype modifies the association between coffee intake and the risk of hypertension. *J. Hypertens.* **27**, 1594–601 (2009).

241. Alfaro, T. M., Monteiro, R. A., Cunha, R. A. & Cordeiro, C. R. Chronic coffee consumption and respiratory disease: a systematic review. *Clin. Respir. J.* (2017). doi:10.1111/crj.12662

242. Clark, I. & Landolt, H. P. Coffee, caffeine, and sleep: A systematic review of epidemiological studies and randomized controlled trials. *Sleep Med. Rev.* (2016). doi:10.1016/j.smrv.2016.01.006

243. Xie, Y. *et al.* Coffee consumption and risk of gastric cancer: an updated meta-analysis. *Asia Pac. J. Clin. Nutr.* **25**, 578–588 (2016).

244. Trembling, P. M. *et al.* Performance of Enhanced Liver Fibrosis test and comparison with transient elastography in the identification of liver fibrosis in patients with chronic hepatitis B infection. *J. Viral Hepat.* **21**, 430–438 (2014).

245. Rosenberg, W. M. C. *et al.* Serum markers detect the presence of liver fibrosis: a cohort study. *Gastroenterology* **127**, 1704–13 (2004).

246. Kinner, S., Reeder, S. B. & Yokoo, T. Quantitative Imaging Biomarkers of NAFLD. *Dig. Dis. Sci.* **61**, 1337–1347 (2016).

247. Graeter, T. *et al.* Coffee consumption and NAFLD: a community based study on 1223 subjects.

BMC Res. Notes **8**, 640 (2015).

248. Delgado-Rodriguez, M. Bias. *J. Epidemiol. Community Heal.* (2004). doi:10.1136/jech.2003.008466

249. Bracken, M. B. *et al.* Heterogeneity in assessing self-reports of caffeine exposure: implications for studies of health effects. *Epidemiology* **13**, 165–71 (2002).

250. Gilbert, R. M., Marshman, J. A., Schwieder, M. & Berg, R. Caffeine content of beverages as consumed. *Can. Med. Assoc. J.* **114**, 205–8 (1976).

251. Ludwig, I. A. *et al.* Variations in caffeine and chlorogenic acid contents of coffees: what are we drinking? *Food Funct.* **5**, 1718–26 (2014).

252. Moeenfard, M., Erny, G. L. & Alves, A. Variability of some diterpene esters in coffee beverages as influenced by brewing procedures. *J. Food Sci. Technol.* **53**, 3916–3927 (2016).

253. Farah, A. *et al.* Chlorogenic Acids and Lactones in Regular and Water-Decaffeinated Arabica Coffees. *J. Agric. Food Chem* **54**, 374–381 (2006).

254. Gross, G., Jaccaud, E. & Huggett, A. C. Analysis of the content of the diterpenes cafestol and kahweol in coffee brews. *Food Chem. Toxicol.* **35**, 547–554 (1997).

255. Ludwig, I. A. *et al.* Extraction of coffee antioxidants: Impact of brewing time and method. *Food Res. Int.* **48**, 57–64 (2012).

256. Moeenfard, M., Rocha, L. & Alves, A. Quantification of Caffeoylquinic Acids in Coffee Brews by HPLC-DAD. *J. Anal. Methods Chem.* 965353 (2014). doi:10.1155/2014/965353

257. Zhang, C., Linforth, R. & Fisk, I. D. Cafestol extraction yield from different coffee brew mechanisms. *Food Res. Int.* **49**, 27–31 (2012).

258. MRC Elsie Widdowson Laboratory. National Diet and Nutrition Survey Years 1-8. 2008/09-2015/16. [data collection] 9th Edition. (2018).

259. National Diet and Nutrition Survey. *Appendix B Methodology for years 7 and 8 of the NDNS RP*. (2018).

260. IBM Corp. IBM SPSS Statistics for Mac. (2016).

261. Morris, J. Why espresso? Explaining changes in European coffee preferences from a production

of culture perspective. *Eur. Rev. Hist. Rev. Eur. d'histoire* **20**, 881–901 (2013).

262. Dosemeci, M., Wacholder, S. & Lubin, J. H. Does nondifferential misclassification of exposure always bias a true effect toward the null value? *Am. J. Epidemiol.* **132**, 746–8 (1990).

263. Schreiber, G. B., Maffeo, C. E., Robins, M., Masters, M. N. & Bond, A. P. Measurement of coffee and caffeine intake: implications for epidemiologic research. *Prev. Med. (Baltim).* **17**, 280–94 (1988).

264. McCusker, R. R., Goldberger, B. A. & Cone, E. J. Caffeine Content of Specialty Coffees. *J. Anal. Toxicol.* **27**, 520–522 (2003).

265. Creswell, J. *Research design: Qualitative, quantitative, and mixed methods approaches*. (Sage, 2013).

266. Bishop, F. L. Using mixed methods research designs in health psychology: An illustrated discussion from a pragmatist perspective. *Br. J. Health Psychol.* **20**, 5–20 (2015).

267. Morgan, D. L. Pragmatism as a Paradigm for Social Research. *Qual. Inq.* **20**, 1045–1053 (2014).

268. Michie, S., Van Stralen, M. M. & West, R. Implementation Science The behaviour change wheel: A new method for characterising and designing behaviour change interventions. *Implement. Sci.* **6**, 42 (2011).

269. Fusch, P. I. & Ness, L. R. Are We There Yet? Data Saturation in Qualitative Research. *Qual. Rep. How To Artic.* **20**, 1408–1416 (2015).

270. Braun, V. & Clarke, V. Using thematic analysis in psychology. *Qual. Res. Psychol.* 77–101 (2006).

271. NVivo qualitative data analysis Software. (2016).

272. Public Health England & Royal Society for Public Health. *Healthy Conversations and the Allied Health Professionals*. (2015).

273. Beate Samdal, G., Eide, G. E., Barth, T., Williams, G. & Meland, E. Effective behaviour change techniques for physical activity and healthy eating in overweight and obese adults; systematic review and meta-regression analyses. *Int. J. Behav. Nutr. Phys. Act.* **14**, 42 (2017).

274. Whatnall, M. C., Patterson, A. J., Ashton, L. M. & Hutchesson, M. J. Effectiveness of brief nutrition interventions on dietary behaviours in adults: A systematic review. *Appetite* **120**, 335–347 (2018).

275. Loftfield, E. *et al.* Association of Coffee Drinking With Mortality by Genetic Variation in Caffeine Metabolism. *JAMA Intern. Med.* **178**, 1086–1097 (2018).

276. Lonardo, A. *et al.* Sex Differences in NAFLD : State of the Art and Identification of Research Gaps. *Hepatology* hep.30626 (2019). doi:10.1002/hep.30626

277. Charters, E. The Use of Think-aloud Methods in Qualitative Research An Introduction to Think-aloud Methods. *Brock Educ. J.* **12**, (2003).

278. Friedrich–Rust, M. *et al.* Performance of Transient Elastography for the Staging of Liver Fibrosis: A Meta-Analysis. *Gastroenterology* **134**, 960-974.e8 (2008).

279. Degos, F. *et al.* Diagnostic accuracy of FibroScan and comparison to liver fibrosis biomarkers in chronic viral hepatitis: A multicenter prospective study (the FIBROSTIC study). *J. Hepatol.* **53**, 1013–1021 (2010).

280. Edwards, P. J. *et al.* Methods to increase response to postal and electronic questionnaires. *Cochrane Database Syst. Rev.* (2009). doi:10.1002/14651858.MR000008.pub4

281. Barlett, J. E., Kotrlik, J. W. & Higgins, C. C. Organizational research: Determining appropriate sample size in survey research. *Inf. Technol. Learn. Perform. Journal; Spring* **19**, 43–50 (2001).

282. Microsoft. Microsoft Excel. (2010).

283. Galle, P. R. *et al. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma q*. (2018). doi:10.1016/j.jhep.2018.03.019

284. Alazawi, W. *et al.* Ethnicity and the diagnosis gap in liver disease: a population-based study. *Br. J. Gen. Pract.* **64**, e694–e702 (2014).

285. Rezayat, A. A. *et al.* Association between smoking and non-alcoholic fatty liver disease: A systematic review and meta-analysis. *SAGE Open Med.* **6**, (2018).

286. Hodge, A. *et al.* Coffee Intake Is Associated with a Lower Liver Stiffness in Patients with Non-Alcoholic Fatty Liver Disease, Hepatitis C, and Hepatitis B. *Nutrients* **9**, 56 (2017).

287. Cornelis, M. C. & Munafo, M. R. Mendelian Randomization Studies of Coffee and Caffeine Consumption. *Nutrients* **10**, (2018).

288. Zhang, Y., Liu, Z., Choudhury, T., Cornelis, M. C. & Liu, W. Habitual coffee intake and risk for nonalcoholic fatty liver disease: a two-sample Mendelian randomization study. *Eur. J. Nutr.* 1–7

(2020). doi:10.1007/s00394-020-02369-z

289. Taylor, A. E., Davey Smith, G. & Munafò, M. R. Associations of coffee genetic risk scores with consumption of coffee, tea and other beverages in the UK Biobank. *Addiction* **113**, 148–157 (2018).

290. Handzlik-Orlik, G., Holecki, M., Wilczyński, K. & Duława, J. Osteoporosis in liver disease: pathogenesis and management. *Ther. Adv. Endocrinol. Metab.* **7**, 128–35 (2016).

291. Nehlig, A. Interindividual Differences in Caffeine Metabolism and Factors Driving Caffeine Consumption. *Pharmacol. Rev.* **70**, 384–411 (2018).

292. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. (American Psychiatric Association, 2013).

293. Meredith, S. E., Juliano, L. M., Hughes, J. R. & Griffiths, R. R. Caffeine Use Disorder: A Comprehensive Review and Research Agenda. *J. Caffeine Res.* **3**, 114–130 (2013).

294. Favrod-Coune, T. & Broers, B. Addiction to Caffeine and Other Xanthines. in *Textbook of Addiction Treatment: International Perspectives* 437–453 (Springer Milan, 2015). doi:10.1007/978-88-470-5322-9_18

295. Rothwell, J. *et al.* A Metabolomic Study of the Variability of the Chemical Composition of Commonly Consumed Coffee Brews. *Metabolites* **9**, 17 (2019).

References