Liver Fibrosis in Psoriasis (LFP) Study

Study Protocol

Protocol

Full Title	Investigation of the prevalence of liver fibrosis in patients with psoriasis using Transient Elastography and evaluation of the relationship between liver fibrosis and risk factors for liver fibrosis including methotrexate.
REC Reference	20/NE/0039
NUTH NHS Trust sponsor's reference	9205
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Sponsored by	The Newcastle Upon Tyne Hospitals NHS Foundation Trust
Logos	NHS The Newcastle upon Tyne Hospitals NHS Foundation Trust

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2. Protocol Signature Page

2.1. Protocol authorisation signatories

Signature…….

Dr Philip Hampton, **Chief Investigator**

2.2. Principal/Chief Investigator signature

I confirm that I have read and understood protocol v1.02 dated 21/08/2019. I agree to comply with the study protocol, the principles of GCP, research governance, and appropriate reporting requirements.

Signature…….

Print Name ……..

Site Name .....

3. Contents:

4. Glossary of Abbreviations

LFP	Liver Fibrosis in Psoriasis
TE	Transient Elastography
MTX	Methotrexate

5. Responsibilities

Sponsor The Newcastle upon Tyne Hospitals NHS Foundation Trust will act as the Sponsor for this study. Day-to-day responsibility for Sponsor-level activities will be delegated to the Principal Investigator.

Funder Psoriasis Association

Trial Management The Study Management group will consist of all of the investigators.

Chief Investigator This is a single-centre study and the Chief Investigator (Dr Hampton) will have overall responsibility for the conduct of the study at this site.

6. Protocol Summary

Short title	Liver Fibrosis in Psoriasis
Principal investigator	Dr Philip Hampton
Sponsor	The Newcastle-upon-Tyne Hospitals NHS Foundation Trust
Funder	Psoriasis Association
Study design	Cross sectional study
Study intervention	Transient Elastography using Fibroscan Assessment of liver fibrosis risk factors
Primary objective	To determine the prevalence of liver fibrosis in patients with psoriasis (LSM >7.9kPa, >7.0 kPa, > 9.5kPa) and to evaluate the relationship between the cumulative dose of methotrexate and liver fibrosis in patients with psoriasis.
Secondary objectives	1. To evaluate the relationship between other liver fibrosis risk factors and non-invasive markers of liver fibrosis in patients with psoriasis using univariate analysis. 2. To perform a power calculation to determine number of participants required for a large multivariable analysis to investigate factors influencing liver fibrosis and determine which risk factors are most important in the development of liver fibrosis.
Primary outcome	To determine the prevalence of liver fibrosis in patients with psoriasis (LSM >7.9kPa, >7.0 kPa, > 9.5kPa) and to evaluate the relationship between the cumulative dose of Methotrexate and liver fibrosis in patients with psoriasis.
Number of study sites	One (the Newcastle upon Tyne Hospitals NHS Foundation Trust)
Study population size	250
Study duration	2 years

7. Introduction

Patients with psoriasis appear to have higher rates of liver fibrosis in comparison to the general population. The higher rates of risk factors for liver fibrosis such as obesity, alcohol and diabetes are important; however there have been concerns that methotrexate can contribute to liver fibrosis. Ever since methotrexate has been used to treat psoriasis there have been concerns over the risk to liver health. Until the 1990s liver biopsies were recommended pre and during MTX therapy. Despite the increasing importance of biologic therapies, methotrexate remains the most commonly used systemic agent in the UK. The majority of patients needing systemic therapy will try methotrexate first as per NICE guidance.

This study aims to investigate the prevalence of liver fibrosis in a group of patients with psoriasis by measuring liver stiffness measurement (LSM) using Transient Elastography (TE), now increasingly used for monitoring of liver fibrosis. The previous standard to monitor liver fibrosis was liver biopsy but concerns over morbidity and mortality along with sampling error have led to a decline in this test being performed. In addition to measuring liver stiffness, the cumulative methotrexate dose and other important factors including BMI, waist circumference and alcohol intake will be recorded. A univariate analysis will be performed to investigate the relationship between all measured risk factors and LSM.

The ultimate goal is to use the prevalence data to perform a power calculation to determine the number of participants required to conduct a study to determine which factors can predict the risk of liver fibrosis. Increasingly experts believe that other risk factors for liver fibrosis such as obesity and alcohol intake may be more important than methotrexate. We want to determine whether or not methotrexate is an independent risk factor for liver fibrosis in patients with psoriasis and if so whether we can predict which populations are most at risk from negative side effects of methotrexate. Using this data a risk prediction model can be built to allow optimal and safe prescribing of methotrexate.

8. Background

Psoriasis is an inflammatory skin disease that typically follows a relapsing and remitting course. The prevalence is estimated to be around 1.3–2.2% in the UK via systematic review [1]. The level of disability caused by psoriasis is as has high as for diabetes, heart failure and some cancers [2]. Comorbidities can be associated with psoriasis including psoriatic arthritis and cardiovascular comorbidities.

Liver fibrosis appears to be more prevalent in patients with psoriasis compared to the normal population. Transient Elastography has been used in observational studies for evaluating the prevalence of liver fibrosis in psoriasis patients. In a recent UK study, the prevalence of advanced liver fibrosis (LSM >9.5 kPa) in patients with severe psoriasis was 14.1% [3]. In a cohort study of 1535 patients, advanced liver fibrosis (LSM >9.5 kPa) was detected in 8.1% of patients with psoriasis and 3.6% of those without psoriasis [4]. In a cross sectional study of 165 patients with psoriasis a raised LSM >7kPa was shown in 11% of patients [5].

Key risk factors for liver fibrosis including obesity, metabolic syndrome and alcohol excess has been shown to be more common in patients with psoriasis. It remains a possibility that the inflammation derived from severe psoriasis alone could have an impact on inflammation in other organs such as the liver [6].

Liver fibrosis has been shown to be higher in psoriasis patients taking methotrexate. In a systematic review of observational studies methotrexate seemed to contribute to development of liver fibrosis in patients with psoriasis. Although the quality of these studies were poor [7]. In a study by Aithal et al, the risk of liver fibrosis was shown to be 8% in psoriasis patients taking a cumulative dose of 6g [8]. Visser et al. demonstrated that 6.3% of patients with rheumatoid arthritis, taking methotrexate developed liver fibrosis over 4.6 years [9]. Interestingly, in a more recent study by Pongpit et al, the cumulative dose of methotrexate was not identified as a risk factor for significant liver fibrosis [5].

The first line systemic therapy for psoriasis is methotrexate. Ciclosporin, acitretin and biologic agents are alternatives if methotrexate is not appropriate or successful. Methotrexate is an antineoplastic antimetabolite with anti-inflammatory and immunosuppressant properties. The exact mechanism of action remains unclear and it is likely that different dosing regimens have different biological effects. The low dose weekly regimen used for psoriasis treatment may work by increasing the level of anti-inflammatory proteins called adenosines or by an effect on cell division due to inhibition of the tetrahydrofolate reductase enzyme. At higher doses, used in chemotherapy regimens, methotrexate works by causing significant inhibition of tetrahydrofolate dehydrogenase and prevents the formation

of tetrahydrofolate, which is necessary for the formation of thymidylate an essential component of DNA. Methotrexate is used in many conditions including psoriasis, psoriatic arthritis, rheumatoid arthritis and Crohn's disease. In chronic plaque psoriasis 50-60% of patients treated with methotrexate see a reduction in PASI score of 75% in 3-6 months [10].

Since the early days of methotrexate treatment for psoriasis there have been concerns regarding liver toxicity. However, a number of confounding factors have always made it unclear whether or not the methotrexate was responsible for the liver fibrosis identified in some patients.

Due to the concerns regarding liver fibrosis and methotrexate the early guidelines recommended pre-treatment liver biopsy and then repeat liver biopsy for every 1.5g cumulative methotrexate. As the use of methotrexate became more widespread the enthusiasm for routine liver biopsies decreased. Data also emerged showing that the development of significant liver fibrosis was highly unlikely with less than 5g cumulative methotrexate [8].

The potential risk associated with liver biopsy led to a search for other less invasive methods of detecting liver fibrosis. Various studies were published in the 1980s and 1990s investigating the use of a biomarker called procollagen three peptide (PIIINP). PIIINP is the amino terminal peptide of type III procollagen, released from the precursor peptide during the synthesis and deposition of type III collagen. PIIINP in the serum can be derived from the synthesis of new type III collagen or from the degradation of existing type III collagen fibrils and therefore has been suggested as a serum marker of liver fibrosis. Serial monitoring of PIIINP has been advocated as a method of monitoring patients on Methotrexate for the development of fibrosis. However, this approach had a number of limitations. Firstly, PIIINP is only a marker of active collagen production and may not identify underlying previous liver fibrosis. Secondly, its use is unreliable in patients with arthritis who have on going cartilage re-modelling with active collagen formation. Up to 40% of psoriasis patients will develop arthritis at some stage, many of whom remain undiagnosed for long periods. It was therefore not surprising that studies investigating the use of PIIINP have shown that it has very poor specificity for liver fibrosis with a positive predictive value as low as 23.4%. In the recent NICE guidelines the evidence for PIIINP as a marker for liver fibrosis in methotrexate treated psoriasis patients was rated as low to very low quality. Due to the methodology of NICE guidelines where the best evidence is used even if it is of low quality, PIIINP is still recommended as a marker for liver fibrosis [11].

Assessment of liver fibrosis

The gold standard investigation for liver fibrosis is liver biopsy, which gives a visual measure of liver fibrosis. Established fibrosis scoring systems such as NIH, NASH, CRN or METAVIR systems typically stage fibrosis from 0 (no fibrosis) to 4 (cirrhosis) [12]. The advantage of liver biopsy is it also helps define the aetiology of liver fibrosis. However, due to its invasive nature liver biopsy is impractical for widespread use. A number of non-invasive fibrosis strategies for fibrosis assessment of varying complexity have been studied and some are now routinely used in clinical practice.

Simple non-invasive markers of liver fibrosis

Hepatocellular dysfunction and portal hypertension result from advancing hepatic fibrosis. This may be reflected in 'routine' blood tests such as liver function tests (low albumin), full blood count (thrombocytopenia) and coagulation profile (prolonged prothrombin time). These tests provide an indirect measure of markers of fibrosis and as they are inexpensive are performed in all patients with liver disease. With increasing liver fibrosis the ALT typically falls and the AST remains stable or rises, and as a result the AST/ALT ratio (AAR) increases and can be a useful simple method of identifying patients with advanced fibrosis. Previous studies identified a cut-off >1 for the AAR as a diagnostic test for cirrhosis [13]. However, a lower cut-off of >0.8 is more sensitive in patients with non-alcoholic fatty liver disease. In a previous study from the unit, an AAR <0.8 had high predictive ability to exclude advanced fibrosis (AUROC 0.83, sensitivity 74%, specificity 78%, negative predictive value (NPV) 93%), but its positive predictive ability was limited (PPV 44%) [14]. Although the AAR is reasonably accurate alone, its accuracy is enhanced when combined with other clinical and biochemical indices.

The FIB-4 score (http://gihep.com/calculators/hepatology/fibrosis-4-score/) is probably one of the best simple non-invasive tests for fibrosis and encompasses the AST, ALT, Age and platelet count. It was originally derived in patients with hepatitis C and HIV co-infection, but has now been well validated in NAFLD [14, 16, 17]. In one study of >500 patients the FIB-4 score had a NPV of 90% at a cut-off of 1.3 for stage 3–4 fibrosis, while the PPV was 80% for stage 3-4 fibrosis at cut-off 2.6 [16]. The FIB-4 score has also been validated in patients with NAFLD with normal ALT levels [18].

The NAFLD Fibrosis Score (www.nafld.score.com) is another simple non-invasive score for fibrosis derived from simple clinical and biochemical indices (age, AST/ALT ratio, albumin, presence or absence of diabetes, BMI and platelet count). This score was developed in a cohort of 733 patients with NAFLD. By applying a low cut-off (<−1.455), advanced fibrosis can be excluded with high accuracy (NPV 93%)

while a high cut-off threshold (>0.676) offers accurate detection of advanced fibrosis (PPV 90%) [19]. While this score has been well validated by several studies since in patients with NAFLD, it has not been assessed in patients with other liver diseases.

Recent work has now demonstrated that the diagnostic accuracy of the FIB-4 and NAFLD fibrosis score can be improved by using age adjusted cut-offs. By using a cut-off of 2.0 for the FIB-4 score and 0.12 for the NAFLD fibrosis score to exclude advanced fibrosis in individual ≥65 year olds significantly reduces the false positive rate, reducing the need for further investigations in this group. Moreover, the FIB-4 score and NAFLD fibrosis score performs poorly in identifying or excluding advanced fibrosis in those aged <35 years old and as such alternative non-invasive tests are needed [20].

Transient elastography (TE; Fibroscan)

TE is being increasingly used to stage liver fibrosis in patients with suspected liver disease and this has reduced the requirement for liver biopsy to stage liver fibrosis in many patients. Liver biopsy is invasive, has limitations as a screening test due to sampling errors and variation in pathological interpretation and is associated with a mortality rate of 0.01%-0.1% [21].

Fibrotic livers have reduced elasticity due to the deposition of fibrous tissue in the hepatic parenchyma. TE gives a 'liver stiffness measurement' (LSM) using pulsed-echo ultrasound as a surrogate marker of fibrosis. The LSM correlates well with the degree of hepatic fibrosis in a range of liver diseases, including NAFLD, hepatitis B, hepatitis C and in patients treated with methotrexate [22]. In a study of 246 patients with biopsy-proven NAFLD, TE achieved high AUROCs for the detection of ≥stage 2 fibrosis, ≥ stage 3 fibrosis and cirrhosis (0.84, 0.93 and 0.95, respectively) and performed better than a number of simple non-invasive scores in the staging of fibrosis. In that study, TE had a high NPV of 96% for ≥ stage 3 fibrosis at a cut-off of 7.9 kPa but only modest PPV (52% at 7.9 kPa and 72% at 9.6 kPa) [23]. A low LSM reliably excludes advanced fibrosis, but the optimum cut-offs for clinical use are yet to be determined. Previous observational studies looking at the prevalence of liver fibrosis and advanced liver fibrosis used LSM >7 kPa and LSM >9.5kPa as their cut-off values [3-5]. However, there are significant limitations to using TE. Results may be invalid in those with central obesity (BMI >35 kg/m2) or type 2 diabetes [24]. For obese patients, the Fibroscan XL probe has been developed that is associated with fewer LSM failures (1.1% vs16%) than the M probe and was accurate for the diagnosis of ≥F2 fibrosis and cirrhosis (AUROC 0.83 and 0.94, respectively) [25]. However, even with the XL probe, 10% of patients with a BMI >28 kg/m2 have a difference of ≥2 fibrosis stages between TE and liver biopsy [26].

Despite its limitations, the usefulness of TE in detecting liver fibrosis in patients with psoriasis has been demonstrated and TE is increasingly recommended to be used in monitoring patients taking methotrexate [4, 21].

9. Objectives

Primary objective

To determine the prevalence of liver fibrosis in patients with psoriasis (LSM >7.9kPa, >7.0 kPa, > 9.5kPa) and to evaluate the relationship between the cumulative dose of methotrexate and liver fibrosis in patients with psoriasis.

Secondary objectives

1. To evaluate the relationship between other liver fibrosis risk factors and non-invasive markers of liver fibrosis in patients with psoriasis using univariate analysis.

2. To perform a power calculation to determine number of participants required for a large multivariable analysis to investigate factors influencing liver fibrosis and determine which risk factors are most important in the development of live fibrosis.

Primary outcome

To determine the prevalence of liver fibrosis in patients with psoriasis (LSM >7.9kPa, >7.0 kPa, > 9.5kPa) and to evaluate the relationship between the cumulative dose of Methotrexate and liver fibrosis in patients with psoriasis.

10. Method and Study Design

The study will be a cross sectional design. Patients with psoriasis with a PASI score of at least 5 and duration of at least 1 year will be invited to join the study.

All of the data that we are interested in is recorded as part of standard clinical care and we do not want to repeat measurements unnecessarily. We will therefore accept values for blood tests that have been recorded within 6 months of patient recruitment and LSM values that have been recorded within 12 months of recruitment to the study.

For patient severity scores and assessments of clinical data such as BMI, these will be collected at the time of recruitment.

The following data will be recorded for each patient:

- Patient demographics: Age, Gender, Ethnicity Socioeconomic status.

- Disease severity: Duration of psoriasis, Age of onset of psoriasis), Year of diagnosis (best approximation), Year first seen by a dermatologist, PASI at recruitment, Worse ever PASI, DLQI at recruitment, worse ever DLQI, Family history of psoriasis (first degree relative such as parent, sibling or child).

- Characteristics: Height and Weight, Body Mass Index (BMI), Waist circumference, smoking status, alcohol intake questionnaire and AUDIT score, Blood pressure , skin type and skin cancer risk factors.

- Liver stiffness measurements: Value, >7.9kPa (yes/no), > 7kPa (yes/no), > 9.5kPa (yes/no).

- Alcohol related questions: AUDIT score, Average alcohol intake in the last year (units per day or units per week)*, A history of sustained excessive alcohol consumption of > 35 units/week for females or > 50units per week for males for more than 1 year, A history of excessive alcohol consumption (>14 units/day for both) – document the average units/day or week and the duration of alcohol, A history of alcohol dependence.

- Comorbidities –has the patient ever had or required treatment for the following illnesses and year of onset of illness:
  Cardiac disease (Heart failure, Cardiac arrhythmias, Stroke , Coronary artery disorders, Angina , Myocardial infarction), Vascular diseases (Hypertension, Peripheral vascular disorders, Deep vein thrombosis, Pulmonary embolism , Disorders of metabolism and nutrition (Diabetes mellitus, Impaired glucose tolerance , Dyslipidaemia , Endocrine diseases (Thyroid disease), Nervous system disorders(Demyelinating diseases ,Epilepsy) , Respiratory, thoracic and mediastinal disorders (Asthma, COPD) , Renal and urinary tract diseases (Chronic renal failure), Hepatobiliary diseases (Viral hepatitis infection, Other liver disease), Gastrointestinal diseases (Peptic ulcer), Gastrointestinal inflammatory conditions (Crohn's disease, Ulcerative colitis), Psychiatric diseases (Depression, Anxiety), Infections and infestations (Tuberculosis). Immune system disorders, Skin and soft tissue disorders (Psoriatic arthritis (Diagnosis of PSA by a rheumatologist? And Year of diagnosis), Other types of cancers: Skin cancers (Non-melanoma skin cancer, Squamous cell, carcinoma, Basal cell carcinoma) Melanoma skin cancers and pre-

cancerous skin lesions (Melanoma skin cancer, Melanoma in situ, Bowen disease, Actinic keratosis, Keratoacanthoma

- Duration on methotrexate in months, cumulative dose of methotrexate
- UV Therapy– (yes/No), duration and type, response

- Any current systemic drug, Oral PUVA or biologics for psoriasis, Small molecule immunomodulator therapy for psoriasis (Apremilast or dimethyl fumarate) – dose, frequency and date started

- All previous systemic or biologics or oral PUVA, small molecule immunomodulator therapy for psoriasis – start and stop dates and stop reason

- Any other systemic drug or biologic drugs (dose and frequency) and durations with start dates and stop dates and duration

- Current medications and start dates – including pimecrolimus or tacrolimus

- Folic acid: Duration and Frequency

- Blood tests: HBA1C, Fasting glucose (if available), Lipid profile including, Triglycerides, HDL cholesterol, AST, ALT, Abnormal AST in the past year, Abnormal ALT in the past year, Worse ever AST/ALT, Platelets, Procollagen three peptide (PIIINP), Albumin.

- Previous liver ultrasound report, Previous liver biopsy report

- NAFLD and Fib4 score will be calculated and metabolic syndrome will be assessed based on the IDF metabolic syndrome definition (modified version will be used when fasting results not available (fasting glucose will be replaced by HBAIC and HDL cholesterol and Triglyceride will be replaced by non-fasting value)

A modified the definition will be used: a non-fasting lipid profile when fasting values are not available or HBA1C will be used when fasting glucose is not available.
https://www.uptodate.com/contents/image?imageKey=ENDO%2F53446&topicKey=PC%2F1784&search=metabolic%20syndrome&rank=1~150&source=see_link

Metabolic syndrome	
	IDF 2006 definition
Required	Waist ≥94 cm (men) or ≥80 cm (women)
	And ≥2 of:
Glucose	≥5.6 mmol/L (100 mg/dL) or diagnosed diabetes
HDL cholesterol	<1.0 mmol/L (40 mg/dL) (men); <1.3 mmol/L (50 mg/dL) (women) or drug treatment for

	low HDL cholesterol
Triglycerides	≥1.7 mmol/L (150 mg/dL) or drug treatment for high triglycerides
Hypertension	≥130/85 mmHg or drug treatment for hypertension
	¶ For South Asia and Chinese patients, waist ≥90 cm (men) or ≥80 cm (women); for Japanese patients, waist ≥90 cm (men) or ≥80 cm (women).

This observational study does not impact patient treatment and has no risk of causing adverse events.

11. Concept

11.1. Quantitative outcome measure

- The prevalence of liver fibrosis in patients with psoriasis (LSM >7.9kPa)
- Assessment of risk factors and non-invasive markers of liver fibrosis

11.2. Qualitative outcome measures

None

11.3. Definition of end of study

Recruitment target achieved.

11.4. Study population

Patients with moderate to severe chronic plaque psoriasis attending the dermatology department at Royal Victoria Infirmary, Newcastle.

11.5. Eligibility Criteria

11.5.1 Inclusion Criteria

- Adults ≥ 18 years of age
- Ability to consent
- Chronic plaque Psoriasis diagnosed by a dermatologist with a PASI ≥ 5

11.5.2 Exclusion Criteria

- Pregnancy
- Potential participants who may have difficulties in adequately understanding written or verbal information in English

11.6. Sampling strategy

Total sample size: 250 (can be increased to up to 500).

As this is a pilot study, this should be an adequate sample to test recruitment and the estimate effect sizes to include in a formal statistical power calculation for a planned larger study.

We are interested to recruit a mix of patients receiving different types of treatment including phototherapy and biologics. We will aim to recruit at least 100 patients who are receiving or have previously received methotrexate.

We will compare our study population to BADBIR population to ensure we demonstrate that our sample is representative.

11.7. Screening, Recruitment and Consent

The research team will be required to obtain patient consent and carry out data management. The data required for the study will be collected as part of patients' standard care.

Screening and recruitment will take place in clinics in the Dermatology Department at the Royal Victoria Infirmary.

11.8. Identification and screening of participants

Participants will be identified from all of the psoriasis clinics including the phototherapy department.

11.9. Recruitment procedures

Recruitment to be undertaken from biologics clinic, PUVA clinic, Psoriasis and drug monitoring clinics and phototherapy department.

11.10. Consent procedures

Face to face consent following participant assessment of patient information.

11.11. Data handling and record keeping

All investigators and study site staff will comply with the requirements of the current Data Protection Act with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles. All medical records will be kept in accordance with Trust policy.

11.12. Statistical Analysis plan

The statistical aspects of this research has been reviewed by an individual with relevant statistical expertise:

Ms Emma Slack, Institute of Health & Society, Newcastle University, 4th Floor , Sir James Spence Institute, Royal Victoria Infirmary, Newcastle upon Tyne, NE1 4LP , 0191 282 1344, emma.slack1@newcastle.ac.uk

Descriptive statistics will be used to describe the prevalence of all data recorded.

We will investigate the relationship between LSM and potential risk factors.

11.13. Analysis Methods

All of the data will be assembled in a spreadsheet that will be designed and checked by our statistical collaborators.

The analysis will be performed including all patients and then the group will be divided based on the PASI score (PASI >10 and PASI <10) and analysis of the separate groups will be performed.

We will calculate the prevalence of liver fibrosis (the proportion of the population affected by liver fibrosis) by dividing the number of participants with liver fibrosis in the study population by the total number of people in study population.

For the analyses we will perform these 3 times using the 3 different cut off values for liver stiffness measurements of 7Kpa, 7.9Kpa and 9.5KpA. There is currently no consensus as to which value is most appropriate. We will therefore analyse using all three.

Regression analyses will carried out, the results of which will be used to inform a power calculation for future research.

- Logistic regression will be used to consider the association between liver fibrosis (yes/no) and methotrexate dose (continuous).
- Linear regression will be used to consider level of liver fibrosis (continuous i.e. independent of cut offs) and methotrexate dose (continuous).
- Regression models will also be used to investigate the relationship between other risk factors (e.g. BMI, waist circumference, alcohol consumption etc.) and liver fibrosis.

Analysis will be carried out in STATA 15.

11.14. Withdrawal of participants

Participants can withdraw their permission for us to use their data at any time.

11.15. Data monitoring, quality control and quality assurance

Internal processes within NUTH will be followed for data monitoring etc in accordance with GCP.

12. Proposed Budget

Table 1: Proposed budget

Budget Items	Allocation	Subtotal Cost
Admin support and other research costs		£1,710.50
Statistical advice stats advice, grade F academic scale	40h + admin	£ 5,039.50
Total cost		£ 6,750.00

13. References

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Appendixes

Case Report Form

Patient Demographics	
Age	years
Sex	M/F
Ethnicity	White/Other
Socioeconomic status	Postcode

Disease Severity	
Duration	
Age of onset	
Year of diagnosis (Best approximation)	
Year first seen by a dermatologist	
PASI at recruitment	
Worse ever PASI	
DLQI at recruitment	
Worse ever DLQI	

Liver Stiffness Measurements	
Value	
>7.9 kPa	
>7 **kPa**	
>9.5 **kPa**	

Relevant past investigations	Date/Outcome
Liver ultrasound	
Liver biopsy	

Characteristics	
Height cm, Weight kg	
Body Mass Index (BMI)	kg m -2
Underweight (< 18.5)	
Normal (18.5–24. 9)	
Overweight (25.0–29.9)	
Obesity class I (30.0–34.9)	
Obesity class II (35.0–39.9)	
Obesity class II (≥ 40.0)	
Waist circumference	Cm
Blood pressure	Systolic mm, diastolic mm
Smoking status	
Never Smoked	
Ex-Smoker	
Current Smoker	
Alcohol intake	

AUDIT Score	
Units per week (in the last year)	
History of excessive alcohol consumption: **>35 units/week (females), >50units/week (males)** **>14units/day (female/male)**	Yes/No Yes/No Yes/No
History of alcohol dependence?	Yes/No

Comorbidities	Yes/no (0/1), year of onset
Cardiac disease	
Heart failure	
Cardiac arrhythmias	
Stroke	
Coronary artery disorders	
Angina	
Myocardial infarction	
Vascular diseases	
Hypertension	
Peripheral vascular disorders	
Deep vein thrombosis	
Pulmonary embolism	
Disorders of metabolism and nutrition	
Diabetes mellitus	Type I/II
Impaired glucose tolerance	
Dyslipidaemia	
Endocrine diseases	
Thyroid disease	
Nervous system disorders	
Demyelinating diseases	
Epilepsy	
Respiratory, thoracic and mediastinal disorders	
Asthma	
COPD	
Renal and urinary tract diseases	
Chronic renal failure	
Hepatobiliary diseases	
Viral hepatitis infection	
Other liver disease	
Gastrointestinal diseases	
Peptic ulcer	
Gastrointestinal inflammatory conditions	
Crohn's disease	
Ulcerative colitis	
Psychiatric diseases	
Depression	
Anxiety	
Infections and infestations	

Tuberculosis	
Immune system disorders	
Skin and soft tissue disorders	
Psoriatic arthritis	
Diagnosis of PSA by a rheumatologist?	
Year of diagnosis	
Other types of cancers	
Skin cancers	
Non-melanoma skin cancer	
Squamous cell carcinoma	
Basal cell carcinoma	
Melanoma skin cancers and pre-cancerous skin lesions	
Melanoma skin cancer Melanoma in situ	
Bowen disease	
Actinic keratosis	
Keratoacanthoma	

UV therapy	No of course, no of treatments, cumulative dose (J/cm2), date known to be accurate
Broadband UVB	
Narrowband UVB	
Total Body PUVA	
Oral Puva	
Topical Puva	
Hand and Foot PUVA	
Oral PUVA	
Topical PUVA	

Medications	
Methotrexate	
Cumulative dose	gram
Duration	Months
Folic acid	Years & Frequency
Other systemic drugs and biologics	Start dates
Ciclosprorin	years
Acitretin	years
Apremilast	
Dimethyl fumerate	
Adalimumab	Years
Etanercept	Years
Ustekinumab	
Secukinumab	
Infliximab	
Other biologics	

Other DMARDS	
Drug treatment for low HDL cholesterol/or raised triglycerides	*For metabolic syndrome definition
Drug treatment for diabetes	*For metabolic syndrome definition
Patients current medications	Date started

Blood tests	
HBA1C	
Lipid profile	
Triglycerides	
HDL	
LDL	
Cholesterol	
Platelets	
Liver function tests	
ALT	
Worse every ALT in the past year	
AST	
Worse every AST in the past year	
ALT/AST ratio	
Albumin	
Procollagen three peptide (PIIINP) – worse value	

Fib 4 score	https://www.mdcalc.com/fibrosis-4-fib-4-index-liver-fibrosis
AST	
ALT	
Platelets	
Age	

NAFLD score	https://www.mdcalc.com/nafld-non-alcoholic-fatty-liver-disease-fibrosis-score
BMI	
Impaired fasting glucose/Diabetes	
ALT	
AST	
Platelet count	
Albumin	

Metabolic syndrome	
	IDF 2006 definition
Required	Waist ≥94 cm (men) or ≥80 cm (women)
	And ≥2 of:
Glucose	≥5.6 mmol/L (100 mg/dL) or diagnosed diabetes
HDL cholesterol	<1.0 mmol/L (40 mg/dL) (men); <1.3 mmol/L (50 mg/dL) (women) or drug treatment for low HDL cholesterol
Triglycerides	≥1.7 mmol/L (150 mg/dL) or drug treatment for high triglycerides
Hypertension	≥130/85 mmHg or drug treatment for hypertension
	¶ For South Asia and Chinese patients, waist ≥90 cm (men) or ≥80 cm (women); for Japanese patients, waist ≥90 cm (men) or ≥80 cm (women).

Description	**Fitzpatrick skin type**
Burns easily, never tans	1
Burns easily, tans minimally	2
Burns moderately, tans gradually	3
Burns minimally, tans well	4
Rarely burns, tans profusely	5
Never burns, deeply pigmented	6

Patient baseline questionnaire