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BMJ Open HEROIC: a 5-year observational cohort study aimed at identifying novel factors that drive diabetic kidney disease: rationale and study protocol

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ABSTRACT

Introduction Diabetic kidney disease (DKD) is the leading cause of end-stage kidney disease worldwide and a major cause of premature mortality in diabetes mellitus (DM). While improvements in care have reduced the incidence of kidney disease among those with DM, the increasing prevalence of DM means that the number of patients worldwide with DKD is increasing. Improved understanding of the biology of DKD and identification of novel therapeutic targets may lead to new treatments. A major challenge to progress has been the heterogeneity of the DKD phenotype and renal progression. To investigate the heterogeneity of DKD we have set up The East and North London Diabetes Cohort (HEROIC) Study, a secondary care-based, multiethnic observational study of patients with biopsy-proven DKD. Our primary objective is to identify histological features of DKD associated with kidney endpoints in a cohort of patients diagnosed with type 1 and type 2 DM, proteinuria and kidney impairment.

Methods and analysis HEROIC is a longitudinal observational study that aims to recruit 500 patients with DKD at high-risk of renal and cardiovascular events. Demographic, clinical and laboratory data will be collected and assessed annually for 5 years. Renal biopsy tissue will be collected and archived at recruitment. Blood and urine samples will be collected at baseline and during annual follow-up visits. Measured glomerular filtration rate (GFR), echocardiography, retinal optical coherence tomography angiography and kidney and cardiac MRI will be performed at baseline and twice more during follow-up. The study is 90% powered to detect an association between key histological and imaging parameters and a composite of death, renal replacement therapy or a 30% decline in estimated GFR.

Ethics and dissemination Ethical approval has been obtained from the Bloomsbury Research Ethics Committee (REC 18-LO-1921). Any patient identifiable data will be stored on a password-protected National Health Services N3 network with full audit trail. Anonymised imaging data will be stored in a ISO27001-certificated data warehouse. Results will be reported through peer-reviewed manuscripts and conferences and disseminated to

Strengths and limitations of this study

- This is the first longitudinal diabetic kidney disease (DKD) study involving a multiethnic cohort of patients that aims to deepen our understanding of the pathophysiological differences and disease phenotypes in patient populations with a high prevalence of diabetes and at moderate/high risk of renal progression.
- Standardised inclusion criteria, patient mix and biopsy proven diagnosis will differentiate The East and North London Diabetes Cohort (HEROIC) from previous DKD studies and will provide insight into the marked clinical heterogeneity of DKD.
- The longitudinal study design coupled with serial collection of clinical data, biological samples and novel imaging parameters will provide a unique platform for future scientific investigation.
- Non-invasive quantitative MRI techniques may provide readily accessible markers of diagnosis, prognosis and treatment effect in patients with DKD.
- The size of study may limit our ability to detect ethnicity-specific associations between risk factors and outcomes.

participants, patients and the public using web-based and social media engagement tools as well as through public events.

INTRODUCTION

Diabetes mellitus (DM) and associated complications are among the biggest global health challenges of the 21st century. In developed countries, owing to advances in early diagnosis and prevention, there have been improvements in DM management and a decline in the incidence of DM complications. However, this progress is overshadowed by the ever-rising absolute numbers of people with DM and the rapidly expanding

prevalence of DM in low-income and middle-income countries.¹

Due to the associated chronic metabolic abnormalities, many patients with DM develop complications as a consequence of microvascular and macrovascular dysfunction,² including DKD. Consequently, DKD is a common complication of DM, with approximately 20% of patients with type 2DM in England and Wales meeting criteria for chronic kidney disease (CKD) when estimated using data from primary care.³ DKD is the leading cause of end-stage kidney disease (ESKD) both in the UK⁴ and throughout the world.⁵ With 42% of all patients with ESKD in the USA having a diagnosis of DKD.⁶

Although the extent of albuminuria is recognised to be a strong predictor of adverse renal and cardiovascular outcomes, clinically, DKD is heterogeneous with respect to presentation, histopathology and rate of progression.⁷ Previous efforts to better understand this variability have been complicated by the inclusion of patients with both CKD and diabetes in studies without histopathological confirmation of disease, despite recognition that up to 40% of kidney biopsies still show histological features of isolated diabetic glomerulosclerosis despite the presence of atypical clinical features of non-DKD.⁸ Moreover, the proposed pathogenic mechanisms that underlie DKD are multifactorial, complex and may include direct metabolic injury (such as hyperglycaemia and dyslipidaemia), microvascular ischaemia, epigenetic reprogramming, disordered cellular repair and inflammation.^{9 10} To date, the majority of published DKD cohort studies have been conducted in homogenous (usually white European) populations, despite clear recognition that ethnicity has an important impact on the prevalence of diabetes and severity of kidney disease.^{11 12} Describing the molecular pathology of kidney dysfunction in ethnically diverse patient groups may facilitate the identification of specific subtypes of DKD, thereby allowing targeted surveillance and treatment.

East and North Central London is one of the most ethnically diverse and socially deprived areas of Europe with a high prevalence of DM and associated complications (figure 1).¹³ The ethnicity of East and North London is distinct from the general population of the UK: the boroughs of London (Camden, Hackney, Islington, Newham, Tower Hamlets, Barnet and Enfield), where HEROIC is primarily recruiting from, have a significantly smaller population of white British people (35% vs 80%) but a much larger population of Asian, Black, mixed race and other (online supplementary table 1). Through longitudinal assessment of a multiethnic patient cohort with biopsy confirmed DKD and at high risk of developing adverse kidney and cardiovascular outcomes (as demonstrated by estimated glomerular filtration rate (eGFR) trajectory and/or levels of proteinuria), The East and North London Diabetes Cohort (HEROIC) aims to describe the natural history of kidney dysfunction and development of associated complications.

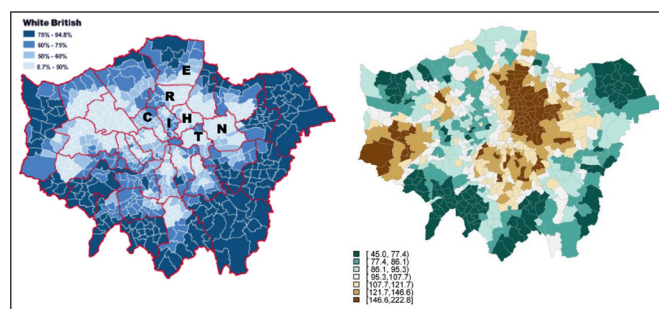


Figure 1 White/non-white population (Asian, black, mixed race and other) of London (left) and deaths due to diabetes (SMR; right, based on 2833 male deaths due to diabetes based on data from the office for national statistics). Camden (C); City and Hackney (H); Enfield (E); Haringey (R); Islington (I); Newham (N) and Tower Hamlets (T). Images reproduced from: <http://www.theguardian.com/graphic/0,5812,1395103,00.html> and <https://www.ucl.ac.uk/ineqcities/atlas/cities/london/disease-specific-mortality/diabetes-mellitus>. SMR, standardised mortality ratio.

Aside from serum markers that allow estimates of kidney function, useful insight into the degree of underlying kidney damage can only be gained by invasive tissue sampling. However, innovative MRI techniques have shown promise in the non-invasive quantification of scarring, as well as providing functional measures of perfusion.¹⁴ Use of serial MRI will allow detailed characterisation of the structural and functional renal^{15 16} as well as cardiac and vascular¹⁷ changes that occur in parallel with progression of DKD (including left ventricular hypertrophy (LVH), myocardial fibrosis and measures of arterial stiffness). Indeed, cardiovascular parameters are of specific interest because, based on other cohort study data, more patients in the HEROIC cohort will die from cardiovascular causes than will reach ESKD.¹⁸ Similarly, detailed assessment of retinal microvasculature by optical coherence tomography angiography (OCT-A)¹⁹ will provide a non-invasive, longitudinal window on microvascular changes that occur in DKD.

OCT-A is a non-invasive technique for imaging the microvasculature of the retina and choroid that uses laser light reflectance of the surface of moving red blood cells to accurately depict the microvasculature through different segmented areas of the eye, thus eliminating the need for intravascular dyes. The procedure is brief, and there are no major associated risks. Swept-source OCT-A (SS-OCT-A) allows different vascular layers, from the superficial and deep retina as well as the choriocapillaris to be individually segmented and analysed.²⁰ OCT-A offers advantages over fluorescein angiography and colour fundus photography as it can detect diabetic retinopathy earlier in the disease, it allows more reliable diagnosis and grading of diabetic retinopathy and its response to treatment and with quantitative measurement of the microvascular changes in the retina may provide insight into the pathophysiology of retinopathy.²¹

Table 1 Primary and secondary objectives of HEROIC

Objective	
Primary objective	To identify histological features of confirmed DKD associated with endpoints in a cohort of patients diagnosed with type 1 and type 2 DM, proteinuria and renal impairment.
Secondary objectives	1. To describe the radiological progression of structural and functional MRI renal parameters in DKD and associate these parameters with disease progression and severity.
	2. To describe the progression of structural and functional cardiac MRI imaging features in DKD and the association of these parameters with disease progression.
	3. To describe the progression of arterial stiffness in DN and the association of these MRI parameters with disease progression.
	4. To investigate the association between MRI-based and histological estimates of kidney fibrosis.
	5. To describe the prevalence of non-diabetic kidney disease in patients referred to secondary care, but otherwise represent an unselected multiethnic patient cohort with diabetes, and either heavy proteinuria or rapidly declining kidney function in East and North London.
	6. To describe the retinal microvascular phenotype and associate these with DKD progression using OCT-A at baseline and at years 1 and 5 of the study.
	7. To generate a biobank of clinical specimens and linked database that will enable additional explorative studies to be undertaken that seek to further identify mechanistic insights and biomarkers associated with DKD progression.

DKD, diabetic kidney disease; DM, diabetes mellitus; DN, diabetic nephropathy; HEROIC, The East and North London Diabetes Cohort; OCT-A, optical coherence tomography angiography.

This offers a further advantage over fluorescein angiography and colour fundus photography.

Finally, establishment of a biobank linking clinical data, biosamples and imaging markers will permit assessment of novel predictors and mediators of disease progression, as well as providing a resource for establishing biological validity using a panel of established urine and blood injury markers. Patients will also consent to future linking of their data to national routine health records to allow capture of long-term follow-up data. The primary and subsidiary aims of HEROIC are outlined in [table 1](#).

In summary, HEROIC is a secondary care-based, multi-ethnic observational study of patients with biopsy-proven DKD. The primary objective is to identify histological features of DKD associated with kidney endpoints in a cohort of patients diagnosed with type 1 and type 2 DM, proteinuria and kidney impairment.

METHODS AND ANALYSIS

Study population and inclusion criteria

HEROIC is a prospective multicentre observational cohort study that will recruit patients with type 1 and type 2 DM primarily from within the seven boroughs of East and North Central London. Patients with moderate or high risk of progression of DKD (see [figure 2](#)) will be invited to take part. After screening, confirmation of DKD will be obtained by kidney biopsy and thereafter participants will be followed annually for up to 5 years. [figure 2](#) illustrates a flow diagram of the referral, screening and enrolment processes. [online supplementary table 2](#) details the full study inclusion and exclusion criteria.

HEROIC recruitment is planned over 24 months or until 500 subjects have been entered into the study. In

addition to patients with DKD, HEROIC will also recruit up to 10 healthy individuals without DKD who will undergo MRI at each site in order to optimise the renal and cardiac MRI protocol before study participants with DKD are imaged. The imaging sequences are not used in standard clinical practise for imaging the kidney and therefore optimisation is necessary. [table 2](#) details the schedule of visits and assessments.

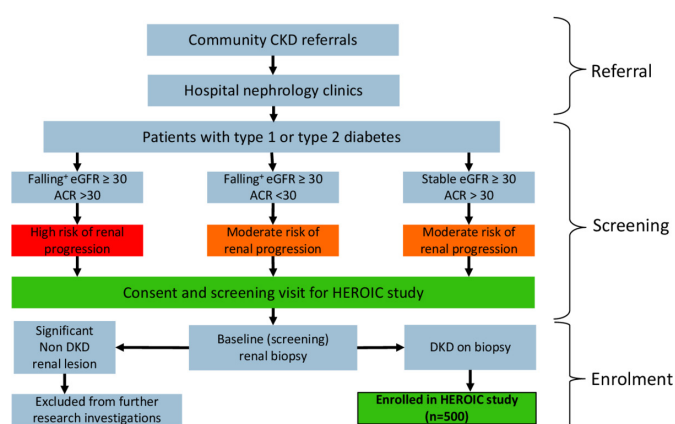


Figure 2 Flow chart of study design that consists of referral, screening and consent of patients with moderate or high risk of renal progression (defined as those with heavy proteinuria uACR >30 mg/mmol, and/or a ≥5 mL/year decline in eGFR calculated across at least three measurements across ≥6 months prior to study enrolment). Screening and enrolment of patients with moderate or high-risk DKD confirmed on renal biopsy. Participants will be followed up annually for up to 5 years. ACR, albumin to creatinine ratio; CKD, chronic kidney disease; DKD, diabetic kidney disease; eGFR, estimated glomerular filtration rate; HEROIC, The East and North London Diabetes Cohort; uACR, urinary ACR.

Table 2 Schedule of visits and assessments

	Screening	Biopsy	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6*†
Day/month			Day 1	Year 1	Year 2	Year 3	Year 4	Year 5
Visit window (days)				±21	±21	±21	±21	±21
Informed consent	x							
Eligibility criteria	x		x					
Demography	x							
Kidney biopsy		x						
Medical history	x		x	x	x	x	x	x
Quality of Life questionnaires			x	x	x	x	x	x
Concomitant medication	x		x	x	x	x	x	x
Physical examination	x		x	x	x	x	x	x
Weight/height/body surface area	x		x	x	x	x	x	x
Vital signs	x		x	x	x	x	x	x
Laboratory blood sample	x		x	x	x	x	x	x
Urine sample	x		x	x	x	x	x	x
ECG and ECHO			x	x				x
measured GFR			x	x				x
MRI‡	x§		x¶	x				x
Retinal screening (OCT-A)			x**	x	x	x	x	x

*Where less than 5 years is available between recruitment and the end of the study the final study visits (month 60) may be brought forward.

†If patients have an additional kidney biopsy for a clinical cause we will perform an additional MRI within 8/52 of biopsy.

‡All MRI visits to be performed at the same time during the day (±2 hours).

§The first five patients recruited at each site will undergo an MRI scan to confirm that the MRI image acquisition is suitable and to optimise the MRI methods that will be used subsequently. ECG and ECHO will be performed in accordance with local protocols and standards of care. Routine haematology and biochemistry measurements will be conducted using the clinical laboratories at Barts Health and the Royal Free London. (Fasting c-peptide (first visit only), fasting cholesterol, FBC, U&E, bone and LFT, 25OH vitamin D, bicarbonate, CRP, glucose, haemoglobin A1c, plasma osmolality, urine creatinine, protein, albumin, sodium, Potassium and urine culture. Day case kidney biopsy will be performed as per routine clinical care. Clinical samples will be processed and reported using internationally accepted protocols.²² Patients will be scanned on two different 1.5 T MR systems (Siemens Healthineers, Erlangen, Germany and GE Healthcare, Milwaukee, Wisconsin, USA). MRI protocols will be similar across both MRI systems. A nuclear medicine (Cr-EDTA) measured GFR will be performed as per standard clinical protocol in parallel to OCT-A and MRI scans. Whole blood, serum, plasma and urine samples will also be biobanked for future use.

¶Baseline MRI to be performed at the earliest 4 weeks, but not later than 12 weeks after kidney biopsy.

**Baseline retinal screening (with SS-OCT-A) will be performed as near to visit 1 as possible (±8/52). Additional yearly retinal screening will be performed using either standard retinal photography or SS-OCT-A to achieve a cost neutral retinal screening programme.

CRP, C reactive protein; DCCT, diabetes control and complications trial; ECHO, echocardiography; FBC, full blood count; LFT, liver function test; SS-OCT-A, swept-source optical coherence tomography angiography; U&E, urea and electrolytes.

Informed consent and study governance

Informed consent will be sought from all participants prior to study entry. Subjects will consent to undertake investigations as set out in the schedule of activities and for long-term access to primary and secondary care follow-up data including blood test results. HEROIC is overseen by a study executive committee that delegates the day-to-day running of the project to an operational steering group.

Study procedures

Study visits will correspond to routine clinic appointments at baseline and will then occur annually for up to 5 years. Study procedures are outlined in [table 2](#).

Biopsy visit

Patients will undergo a kidney biopsy at the start of the study. The risks and benefits of undergoing a kidney

biopsy, including a biopsy being conducted for research purposes, will be discussed with each individual. Patients will attend their local study centre for a kidney biopsy as per standard clinical practice with follow-up in 1 of 2 medical centres.

The biopsy will be reported and scored according to an established pathological classification of DKD.²² This classification leads to a score on up to five dimensions (glomerular, interstitial inflammation, fibrosis, small and large vessels) each scored between 0 and either 2, 3 or 4. Given the range of inclusion criteria, we would expect a range of diabetes-induced glomerular, interstitial and vascular pathology to be evident. If there are other features seen on the biopsy that suggest an additional non-diabetic kidney disease phenotype requiring active intervention (eg, membranous nephropathy or renal

amyloidosis), then these patients will be excluded from the study.

MRI procedure

The baseline MRI scan will occur up to 12 weeks after a kidney biopsy. MRI assessment variables for kidney and cardiac function, morphology and arterial stiffness are outlined in online supplementary table 3. MRI data acquisition will be prioritised in the following order: kidney, cardiac and arterial stiffness. The total scan time for the full imaging protocol is estimated to be approximately 45 min. To minimise physiological variations, patients will be asked to drink at least 250 mL water within the hour immediately before the scan to better standardise hydration status. Patients will also be instructed to abstain from products containing nicotine, alcohol and caffeine for at least 6 hours prior to the scan. All static images will be subjected to a radiological assessment by qualified medical personnel at each MRI site for any incidental findings. Pseudonymised images will be sent to Antaros Medical (Sweden) for analysis of study endpoints using a dedicated software package and certified image analysts. MRI image analysis will be performed blinded to all personally identifiable information as well as clinical and histological makers.

Retinal imaging

Images will be obtained at similar time points to the MRI scans with the Triton OCT Platform (Topcon, Tokyo, Japan). SS-OCT-A is a non-invasive technique obtaining cross-sectional and en-face high resolution images of the retina and choroid. The higher wavelength allows in depth visualisation of all retinal and choroidal layers in high resolution.²⁰ Patients will have non-invasive structural posterior pole OCT imaging collected at the same time as the SS-OCT-A. Patients will continue to undergo fundus photography annually as part of their standard of care diabetic retinopathy screening. OCT-A assessment variables are outlined in online supplementary table 3.

The SS-OCT-A and SS-OCT images will be acquired according to a standard protocol within 8 weeks of baseline, at 1 year and 5 years. The thickness and features of the retinal and choroidal sublayers will be assessed on structural cross-sectional and en face OCT imaging.²³ OCT-A parameters that will be assessed include the foveal avascular zone area and circulation, intercapillary areas and vessel densities^{19 24} at the retinal vascular layers and the choriocapillaris layers (signal voids).²⁰ Juxtaposition with fundus images will allow the colocalisation of findings.

Analysis

Primary and secondary outcome variables are outlined in online supplementary table 4. The primary outcome is time to the composite of death, renal replacement therapy or 30% decline in eGFR

Sample size

Five hundred patients will be recruited to HEROIC with 10 additional healthy volunteers. This is an exploratory and hypothesis generating observational study and this sample size is based on pragmatic considerations. This, the number that could be feasibly recruited, and the investigations performed, given time constraints of the study along with local capacity.

However, to provide some context, we estimate we will have 90% power to detect associations between the histological scores²² and the primary endpoint. For example, assuming a binary histological parameter (eg, vascular score coded as high vs low, eg, a score of 2, 'more than one area of arteriolar hyalinosis', versus 0 or 1 'one or no areas'²²), which 20% of the population experience, associated with an HR of 2.0 for the primary outcome (which we assume will occur in 40% of the total study population), the sample size of 500 would provide 92% power to detect an association at $\alpha=0.01$. Furthermore, we also predict there will be substantial power to detect associations (eg, perfusion index coded as low vs high on kidney MRI parameters) with estimated or measured GFR decline over time. Details of these secondary analyses are presented in the supplementary materials.

Ethics and dissemination

Ethical approval has been obtained from the Bloomsbury Research Ethics Committee (REC 18-LO-1921). Any patient identifiable data will be stored on a password protected National Health Service N3 network with full audit trail. Anonymised imaging data will be stored in a ISO27001 certificated data warehouse.

Patient and public involvement

Patients were not directly involved in the development of the study, design or implementation; however, all patient facing documents were presented to patients attending the Royal London Hospital for their feedback, and amendments were made accordingly. Patient and public engagement events and study result dissemination are planned during the study and following completion.

DISCUSSION

Clinically, DKD is characterised by progressive kidney damage reflected by increased albuminuria, impairment in kidney function (decline in eGFR), elevated blood pressure and excess morbidity and mortality due to cardiovascular complications. The classification of DKD based on albuminuria and eGFR level is simple, affordable, accessible in daily clinical practice, provides prognostic information and is helpful to guide therapeutic decisions but is not without shortcomings. Not all patients with impaired kidney function (eGFR <60 mL/min per 1.73m^2) or significant albuminuria progress to ESKD or develop cardiovascular disease (reviewed in refs 25 26), and there remains a high degree of heterogeneity in the clinical presentation, histopathology, rate of progression and complications of disease. The clinical need

for more specific diagnostic and prognostic tools in early and late stages of DKD and improved biomarkers that can determine the aetiology of the kidney disease and characterise the dominant pathophysiological process in individual patients are required.

HEROIC is the first study of its kind to standardise inclusion criteria by only including patients with biopsy proven DKD from a multiethnic population. This not only allows an affirmative diagnosis of DKD based on histological analysis of tissue samples^{22 27} but will also help to characterise the range of pathological features of kidney disease in patients with diabetes^{28 29} and provides a basis for correlating histology with the clinical phenotype of DKD. The potential for renal biopsies to identify alternative renal pathologies will also serve to benefit patients enrolled in this study by potentially altering the clinical management of their kidney disease. However, renal biopsy has disadvantages: it is invasive (causing discomfort and risking complications), it is susceptible to sampling bias (only ~0.002% of the total glomeruli of one kidney) and it is difficult to perform repeatedly to assess serial changes.

MRI is emerging as a promising non-invasive imaging tool to address these challenges. Renal MRI may complement or even provide an alternative to kidney biopsies, with the advantage of separate evaluation of both kidneys in their entirety, avoiding the sampling bias associated with a kidney biopsy, as well as allowing for detection of regional variations. MRI also provides a variety of imaging parameters that can differentiate pathological from healthy tissues, according to biophysical changes that have been linked to hemodynamics, interstitial fibrosis, tissue inflammation, perfusion, filtration and tissue oxygenation.¹⁶ The association of kidney imaging parameters with histological measures of fibrosis, inflammation, peritubular capillary density and podocyte loss, as well as OCTA-A data, blood or urinary markers of kidney dysfunction, metabolic disturbance and inflammation will be a key aspect of HEROIC.

Central to HEROIC is the establishment of a bioresource through serial collection of biological samples, which will permit assessments of combinations of genetic, molecular and imaging biomarkers, and ultimately link clinical data with biosamples and MRI parameters. This approach may identify novel makers of kidney disease and its progression and uncover key mechanistic pathways underlying the pathogenesis of DKD. Use of panels of urine and blood injury markers will also provide an additional means of establishing biological validity of MRI measures in DKD.

During the course of this study, patients will also be seen in a comprehensive DKD clinic providing them with access to high-quality clinical care, as well as potentially providing access to interventional research studies.

Limitations

Given the 'deep' phenotyping of study participants, the sample size is moderate, which may limit the power to detect associations in stratified analyses (eg, by ethnicity). In addition, although the inclusion criteria are broad by design, not all patients with DKD will be recruited, and the findings from HEROIC may not be generalisable to all those excluded on

the basis of the initial biopsy or who are unwilling to undergo this procedure who may be at low-risk of progression. Specifically those with low-level proteinuria and stable eGFR, who may not progress to ESRD but nonetheless at high risk of CV complications, will not be included.

Furthermore, although loss of kidney function is typically relatively rapid in those with DKD and moderate to heavy proteinuria, it is possible that eGFR decline rates are retarded by the high-intensity multidisciplinary care provided to participants in HEROIC, thereby reducing the power to detect associations between MRI parameters and adverse kidney outcomes. Finally, although the retinal imaging approaches are 'state of the art', the peripheral retina cannot easily be visualised with current commercially available SS-OCTA technology, meaning that informative findings from the peripheral retinal vasculature may be missed.

Summary paragraph

HEROIC is the first study multiethnic longitudinal study with standardised inclusion criteria of patients with biopsy proven DKD. This work will provide insight into the relationships between invasive and non-invasive assessment of kidney parameters and will characterise the cardiac and vascular associations of progressive DKD and also be a unique bioresource for the further investigation of broader aetiopathogenesis of DKD.

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Contributors KM, MMY and BCa conceived the study proposal. KM, MMY, BCa, PH, VP, HM, RU, BCh designed the study rationale, outcome and goals. KM, MMY, BCa, PH, DW, SH, SLF, JH, RK, NA, VP, HM, RU, AS, TAC, LJ, BCh and AKS provided advice and input on the final protocol submission. SK drafted the initial manuscript with input from KM, BCa, BCh, PH, LJ, HM and VP. All authors proof read and approved the final manuscript.

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Competing interests BCh, RU, SK, SH and AKS are employees of AstraZeneca, and authors PH and JH are employees of Antares Medical.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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REFERENCES

- 1 NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4.4 million participants. *Lancet* 2016;387:1513–30.
- 2 Forbes JM, Cooper ME. Mechanisms of diabetic complications. *Physiol Rev* 2013;93:137–88.
- 3 Partnership THQI. National diabetes audit: complications and mortality NHS: NHS digital, 2017. Available: https://files.digital.nhs.uk/pdf/4/t/national_diabetes_audit_2015-16_report_2a.pdf
- 4 Gilg J, Methven S, Casula A, et al. UK renal registry 19th annual report: chapter 1 UK RRT adult incidence in 2015: national and Centre-specific analyses. *Nephron* 2017;137:11–44.
- 5 Toth-Manikowski S, Atta MG. Diabetic kidney disease: pathophysiology and therapeutic targets. *J Diabetes Res* 2015;2015:1–16.
- 6 Stoumpos S, Jardine AG, Mark PB. Cardiovascular morbidity and mortality after kidney transplantation. *Transpl Int* 2015;28:10–21.
- 7 Karalliedde J, Gnudi L. Diabetes mellitus, a complex and heterogeneous disease, and the role of insulin resistance as a determinant of diabetic kidney disease. *Nephrol Dial Transplant* 2016;31:206–13.
- 8 Soni SS, Gowrishankar S, Kishan AG, et al. Non diabetic renal disease in type 2 diabetes mellitus. *Nephrology* 2006;11:533–7.
- 9 A/L B Vasanth Rao VR, Tan SH, Candasamy M, et al. Diabetic nephropathy: an update on pathogenesis and drug development. *Diabetes Metab Syndr* 2019;13:754–62.
- 10 Arora MK, Singh UK. Molecular mechanisms in the pathogenesis of diabetic nephropathy: an update. *Vascul Pharmacol* 2013;58:259–71.
- 11 Nelson RG, Pavkov ME, Hanson RL, et al. Changing course of diabetic nephropathy in the Pima Indians. *Diabetes Res Clin Pract* 2008;82:S10–14.
- 12 Pavkov ME, Knowler WC, Hanson RL, et al. Diabetic nephropathy in American Indians, with a special emphasis on the Pima Indians. *Curr Diab Rep* 2008;8:486–93.
- 13 Mathur R, Noble D, Smith D, et al. Quantifying the risk of type 2 diabetes in East London using the QDScore: a cross-sectional analysis. *Br J Gen Pract* 2012;62:e663–70.
- 14 Debatin JF, Ting RH, Wegmüller H, et al. Renal artery blood flow: quantitation with phase-contrast MR imaging with and without breath holding. *Radiology* 1994;190:371–8.
- 15 Cox EF, Buchanan CE, Bradley CR, et al. Multiparametric renal magnetic resonance imaging: validation, interventions, and alterations in chronic kidney disease. *Front Physiol* 2017;8:696.
- 16 Selby NM, Blankstijn PJ, Boor P, et al. Magnetic resonance imaging biomarkers for chronic kidney disease: a position paper from the European cooperation in science and technology action PARENCHIMA. *Nephrol Dial Transplant* 2018;33:ii4–14.
- 17 van der Meer RW, Diamant M, Westenberg JJM, et al. Magnetic resonance assessment of aortic pulse wave velocity, aortic distensibility, and cardiac function in uncomplicated type 2 diabetes mellitus. *J Cardiovasc Magn Reson* 2007;9:645–51.
- 18 Gansevoort RT, Correa-Rotter R, Hemmelgarn BR, et al. Chronic kidney disease and cardiovascular risk: epidemiology, mechanisms, and prevention. *Lancet* 2013;382:339–52.
- 19 Cheung CY, Tang F, Ng DS, et al. The relationship of quantitative retinal capillary network to kidney function in type 2 diabetes. *Am J Kidney Dis* 2018;71:916–8.
- 20 Spaide RF, Fujimoto JG, Waheed NK, et al. Optical coherence tomography angiography. *Prog Retin Eye Res* 2018;64:1–55.
- 21 Khadamy J, Abri Aghdam K, Falavarjani KG. An update on optical coherence tomography angiography in diabetic retinopathy. *J Ophthalmic Vis Res* 2018;13:487–97.
- 22 Tervaert TWC, Mooyaart AL, Amann K, et al. Pathologic classification of diabetic nephropathy. *J Am Soc Nephrol* 2010;21:556–63.
- 23 Kocasarac C, Yigit Y, Sengul E, et al. Choroidal thickness alterations in diabetic nephropathy patients with early or no diabetic retinopathy. *Int Ophthalmol* 2018;38:721–6.
- 24 Lee D-H, Yi HC, Bae SH, et al. Risk factors for retinal microvascular impairment in type 2 diabetic patients without diabetic retinopathy. *PLoS One* 2018;13:e0202103.
- 25 Persson F, Rossing P. Diagnosis of diabetic kidney disease: state of the art and future perspective. *Kidney Int Suppl* 2018;8:2–7.
- 26 Ioannou K. Diabetic nephropathy: is it always there? assumptions, weaknesses and pitfalls in the diagnosis. *Hormones* 2017;16:351–61.
- 27 Penescu M, Mandache E. The value of kidney biopsy in diabetes mellitus. *Rom J Morphol Embryol* 2010;51:13–19.
- 28 Li L-S, Liu Z-H. Epidemiologic data of renal diseases from a single unit in China: analysis based on 13,519 renal biopsies. *Kidney Int* 2004;66:920–3.
- 29 Haas M, Spargo BH, Wit EJ, et al. Etiologies and outcome of acute renal insufficiency in older adults: a renal biopsy study of 259 cases. *Am J Kidney Dis* 2000;35:433–47.