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Is hyperfiltration associated with higher urine albumin-to-creatinine ratio at follow up among Indigenous Australians? The eGFR follow-up study

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ABSTRACT

Background: Glomerular hyperfiltration is not able to be detected in clinical practice. We assessed whether hyperfiltration is associated with albuminuria progression among Indigenous Australians at high risk of diabetes and kidney disease to determine its role in kidney disease progression.
Methods: Longitudinal observational study of Indigenous Australians aged ≥18 years recruited from >20 sites, across diabetes and/or kidney function strata. At baseline, iohexol clearance was used to measure glomerular filtration rate (mGFR) and hyperfiltration was defined as (i) a mGFR of ≥125 mL/min/1.73 m^2, and (ii) an age-adjusted definition, with the top 10% of the mGFR for each 10 year age group at baseline. Baseline and follow-up urine albumin-to-creatinine ratio (uACR) was collected, and linear regression was used to assess the associations of hyperfiltration and uACR at follow up.
Results: 407 individuals (33% men, mean age 47 years) were followed-up for a median of 3 years. At baseline, 234 had normoalbuminuria and 173 had albuminuria. Among participants with normoalbuminuria, those with mGFR ≥125 mL/min/1.73 m^2 had 32% higher uACR at follow-up ($p = 0.08$), and those with age-adjusted hyperfiltration had 60% higher uACR ($p = 0.037$) compared to those who had normofiltration. These associations were independent of uACR at baseline, but attenuated by HbA_{1c}. Associations were stronger among those without than those with albuminuria at baseline.
Conclusions: Although not available for assessment in current clinical practice, hyperfiltration may represent a marker of subsequent albuminuria progression among individuals who have not yet developed albuminuria.

1. Introduction

Indigenous populations, including Indigenous Australians, experience very high rates of both type 2 diabetes and kidney disease.[1–3] Diabetes is the leading cause of end stage kidney disease in Australia. Up to 77% of Indigenous Australians diagnosed with end stage kidney disease have diabetes as a co-morbidity compared to 33% of non-Indigenous Australians with end stage kidney disease.[4] Early diabetes has been

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characterised by elevated glomerular filtration. It is thought that the processes that occur during hyperfiltration may have a detrimental effect on the kidney.[5] However, the significance of hyperfiltration in terms of causing or predicting the development of albuminuria and chronic kidney disease remains uncertain.

Several structural and functional changes, including hyperfiltration (early on) and increased albuminuria (later on) may be associated with the development of chronic kidney disease (CKD) in patients with diabetes.[6–9] The presence of albuminuria is an important and well recognized risk factor for the development of CKD, particularly in Indigenous Australians[10,11] and in other Indigenous populations across the world including in Pima Indians with diabetes.[12] The association of albuminuria with accelerated glomerular filtration rate (GFR) loss has been confirmed in several studies,[13,14] and the CKD classification incorporates albuminuria stage along with the estimated GFR.[15] Although the majority of people with diabetes follow a classical albuminuria-based pathway,[8] normoalbuminuric progression of diabetic kidney disease is also recognized.[8,16]

The significance of hyperfiltration in terms of causing or predicting the development of albuminuria and CKD remains uncertain as previous studies report conflicting findings, partly due to methodological problems associated with accurately measuring true GFR in the hyperfiltering range, and also due to a lack of studies utilising measured GFR with sufficient long term follow-up.[17] Evidence that hyperfiltration has a pathological impact on renal function has mostly been elucidated from animal studies.[18] In humans, some,[19] but not all,[20] studies have demonstrated an association between the presence of hyperfiltration at baseline and higher follow-up urine albumin-to-creatinine ratio (uACR). Most studies involve individuals with type 1 diabetes,[19–22] and fewer studies have assessed the contribution of hyperfiltration to progression of albuminuria among individuals with type 2 diabetes.[23] The limitations of the studies on participants with type 2 diabetes include small sample sizes,[24,25] use of estimated GFR (eGFR) instead of measured GFR (mGFR)[26] and the inclusion of participants with pre-existing albuminuria,[23] making it difficult to assess the temporal association between hyperfiltration and albuminuria progression.

There are no studies assessing the relationship between hyperfiltration and albuminuria progression in Indigenous Australians, who have a very high prevalence of diabetes and kidney disease. Previously, we have shown in Indigenous Australians that albuminuria is a strong predictor of eGFR decline,[27] and demonstrated that the prevalence of hyperfiltration varied from 7% to 27% depending on the definition of hyperfiltration employed.[28] Furthermore, while hyperfiltration was more prevalent among those with, than those without type 2 diabetes, a significant proportion of those with intermediate hyperglycaemia also had hyperfiltration,[28] suggesting that hyperfiltration may be associated with metabolic abnormalities before diabetes is diagnosed.

In this analysis of longitudinal data from the eGFR study cohort, we now aim to assess the temporal associations between baseline hyperfiltration determined from directly measured GFR, and uACR at follow-up, after considering baseline uACR, HbA_{1c} and other covariates. As it is likely that those with pre-existing albuminuria may already be on a pathway for albuminuria progression, we chose to undertake analyses separately in those with normoalbuminuria and albuminuria at baseline. We hypothesized that in this population with a high burden of metabolic syndrome, diabetes and kidney disease, the presence of hyperfiltration at baseline will be associated with an increased risk of greater uACR at follow up.

2. Materials and methods

2.1. Participants

The eGFR study is a prospective observational study of Indigenous Australians who were recruited from over 20 sites among various regions of Australia.[29] A convenience sample of participants were recruited across five pre-defined strata of diabetes status and kidney function between 2007 and 2011 from primary care facilities, hospital specialist clinics and the general community.[28] The initial aim of the study was to assess the accuracy of the equations used to estimate the GFR, and the study found that the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation provided an unbiased and accurate estimate of GFR in Indigenous Australians.[30] Participants were invited to a follow-up health examination at 2–4 years; and if unavailable, vital status, progression to renal-replacement therapy and serum creatinine were obtained from medical records.[27]

An Indigenous Australian was defined as a person who fulfilled the criteria according to the Australian National Census.[31] Participants with rapidly changing kidney function, those receiving dialysis, women who were pregnant or breastfeeding and those who had a history of allergy or adverse reaction to iodine-based contrast media were excluded from the study. Participants with proteinuria were not excluded, but the majority (87%) of participants with proteinuria by dipstick analysis also had albuminuria.[29] Informed consent was obtained at baseline and follow-up.[27,29]

2.2. Measurement of reference GFR (mGFR)

Using iohexol clearance, GFR was measured at baseline in all participants.[29] Non-isotopic iohexol was injected into an antecubital vein and flushed with 10 mL of normal saline.[28] Venous blood samples were collected from the contra-lateral arm for the measurement of iohexol at 120, 180 and 240 min post injection.[29] Iohexol was measured by Austin Health, Melbourne, Australia using a validated high-performance liquid chromatography (HPLC) assay modified from Niculescu- Duvaz et al.[32] Plasma samples were extracted using a solution of 5% perchloric acid containing internal standard (sodium diatrizoate). Chromatographic separation was achieved using a Microsorb MV C18 5 μ column (Varian Australia) and detection at 244 nm. Analyte concentrations were calculated by comparison to multipoint linear standard curves derived from plasma samples spiked to contain between 3.125 and 800 μg/mL Iohexol (reference material, US Pharmacopoeia). The lower limit of quantitation was 3.125 μg/mL. Intra- and inter-assay performance was assessed using donor plasma spiked with low (20 μg/mL), medium (100 μg/mL) and high (400 μg/mL) concentrations of Iohexol. Precision studies showed a coefficient of variation of 1.0% or less, and inaccuracy ±4.5% or less.[29] Many of the research centres for the eGFR study were located in remote settings, and it was important to use a reference GFR method that was accurate, practical and acceptable to participants. Slope-intercept GFR was calculated and this value was multiplied by 1.73 and divided by the body surface area (BSA). The BSA-slope intercept GFR value (mL/min/1.73 m^2) was corrected by the Brochner-Mortensen correction factor providing a reference GFR value (mL/min/1.73 m^2).

2.3. Baseline clinical and biochemical characteristics

Baseline assessment also included measurements of height, weight, waist and hip circumference. Participants were requested not to consume meat on the day of the examination. Seated blood pressure was measured three times and the mean was calculated (Welch Allyn Medical Products, Skaneateles Falls, USA).[28,29] Non-fasting lipids (triglycerides, total and HDL cholesterol) and HbA_{1c} were determined from the 120 min venous sample for the Iohexol. Additionally, a random spot urine albumin: creatinine ratio (uACR), smoking and anti-hypertensive medication use were collected from routine clinical data and local accredited pathology services.[29] Diabetes was defined as a self-reported diagnosis of diabetes, confirmed from medical records or with a HbA_{1c} ≥ 48 mmol/mol (≥6.5%), and for those without diabetes, intermediate hyperglycaemia was classified if HbA_{1c} ≥ 39 mmol/mol (≥5.7%) and <48 mmol/mol (<6.5%), and normal glycaemia as HbA_{1c} < 39 mmol/mol (<5.7%).[33] Albuminuria categories at baseline were: normoalbuminuria, <27 mg/g (3 mg/mmol); and albuminuria, ≥27 mg/g (3 mg/mmol).[27]

2.4. Follow-up outcome

The follow-up study examination was conducted 2 to 4 years following baseline.[27] Follow-up uACR was determined from a random spot urine sample and collected from local pathology providers. Participants with follow-up time < 6 months were excluded.[27]

2.5. Statistical analysis

Participant characteristics at baseline for those with and without albuminuria at baseline were compared using χ^2 for categorical variables and one-way analysis of variance or Wilcoxon rank-sum tests for continuous variables. Continuous risk factors were normally distributed, except for triglycerides, which was transformed by taking the natural logarithm prior to analysis.

Currently there is no consensus on an mGFR cut-off that represents the state of hyperfiltration.[34] Thus, hyperfiltration at baseline was defined using two criteria: (i) mGFR of ≥125 mL/min/1.73 m^2 with body surface area (BSA) correction irrespective of age, (ii) age-adjusted definition using the 10th centile of mGFR in each 10 year age group at baseline, to incorporate the additional effect of age on mGFR. As age increases mGFR decreases, due to nephrosclerosis which occurs during ageing.[35]

Univariate associations of hyperfiltration, uACR, glycaemia and other baseline risk factors with follow-up uACR were assessed using linear regression. Since the outcome of follow-up uACR was modelled on the log scale due to its non parametric nature, results from regression models were also described as percent increase (for positive beta coefficients) or decline (for negative beta coefficient) of follow-up uACR corresponding to an increase of a unit in each of the independent continuous variable or comparing levels for categorical variables. Multivariate models were assessed to ascertain whether the associations between hyperfiltration and follow-up uACR remained after adjusting for the known baseline covariates of age and gender (model 1), model 1 + baseline uACR (model 2) and model 2 + baseline HbA_{1c} (model 3). Additionally, the influence of the baseline covariates of waist-to-hip ratio, smoking, blood pressure, anti-hypertensive medication use and lipidaemia were also assessed. The variance explained by each model was assessed with the R^2 statistic. Sensitivity analyses were undertaken by (i) repeating the analyses and additionally adjusting for height as a surrogate for nephron number[36] and (ii) using absolute mGFR without the body surface area correction to determine the hyperfiltration groups, as body surface area normalisation may have led to inaccurate GFR measurement in participants with obesity in our study.[37] There was no evidence of multicollinearity between covariates for any of the fitted models (variance inflation factor < 2 for all independent variables).[38] Non-linearity of the association between mGFR and uACR at follow-up was assessed by (i) plotting adjusted mean follow-up uACR values for categories of baseline mGFR (<60, 60–89, 90–124, 125–134, ≥135 mL/min/1.73 m^2) among those with and without baseline albuminuria; and (ii) using the likelihood ratio test to compare a model (adjusted by age, gender and baseline uACR(log)) with a categorical variable of mGFR to an adjusted model with mGFR entered as a linear term. Interactions between each of the hyperfiltration variables with albuminuria or diabetes status at baseline were assessed by comparing log-likelihood ratios of models with and without the interaction terms, after adjusting for baseline sex and age. Statistical analysis was performed using Stata v14 (Stata Corporation, College Station, TX).

3. Results

3.1. Baseline characteristics

There were 654 Indigenous Australian participants in the baseline eGFR study,[28] of whom 520 participants had both baseline and follow up uACR with a median of 3 years follow-up.[25] Of these, 407 participants (38% men, mean age 47 years) also had mGFR at baseline and were thus included in this analysis. Among the 234 with normoalbuminuria at baseline, 94 (74%) had intermediate hyperglycaemia and 66 (36%) had diabetes, and among the 173 with albuminuria at baseline, 33 (26%) had intermediate hyperglycaemia and 117 (64%) had diabetes.

Baseline characteristics according to those with and without albuminuria at baseline are outlined in Table 1. Overall, 19% had glomerular hyperfiltration with mGFR ≥125 mL/min/1.73 m^2, and 11% had hyperfiltration on the age-adjusted definition. The proportion of those with hyperfiltration was greater among those without than those with albuminuria at baseline, whereas the proportion of those with mGFR <90 mL/min/1.73 m^2 was greater among those with albuminuria at baseline.

Significant interactions were observed between each of the hyperfiltration definitions and baseline albuminuria status after adjusting for age and sex ($p < 0.002$ for all comparisons). We did not observe significant interactions between any of the hyperfiltration definitions and baseline diabetes status ($p > 0.3$ for all comparisons). Regression models were therefore stratified by baseline albuminuria status (normoalbuminuria compared to albuminuria).

3.2. Associations between hyperfiltration and uACR at follow-up

In unadjusted analyses, Table 2 shows that among those with normoalbuminuria at baseline, hyperfiltration defined as mGFR ≥125 mL/min/1.73 m^2 showed a borderline association with a higher uACR at follow-up, and hyperfiltration using the age-adjusted definition was significantly associated with higher uACR at follow-up. Among those with albuminuria at baseline, hyperfiltration defined as mGFR ≥125 mL/min/1.73 m^2 was not associated with higher uACR at follow-up, and age-adjusted hyperfiltration showed a borderline association. In those with baseline albuminuria, mGFR <90 mL/min/1.73 m^2 was significantly associated with higher uACR at follow-up. Baseline factors significantly associated with higher uACR at follow-up, irrespective of baseline albuminuria status, included: diabetes, higher HbA_{1c}, higher triglycerides, greater waist-to-hip ratio, and anti-hypertensive medication use.

Fig. 1 shows a non-linear relationship between categories of baseline mGFR and adjusted mean follow-up uACR among those with and without albuminuria at baseline. Attenuation of this relationship by adding HbA_{1c} to a model with age, gender, baseline uACR was greater among those with baseline albuminuria than among those without albuminuria. The likelihood ratio tests showed that the non-linear relationship between mGFR and follow-up uACR was significant for those with normoalbuminuria at baseline ($p = 0.003$), but not for those with albuminuria at baseline ($p = 0.315$).

Among those with normoalbuminuria at baseline, hyperfiltration (irrespective of the criteria used) remained significantly associated with higher uACR at follow-up compared to eGFR ≥90 mL/min/1.73m^2 and not in the hyperfiltration range after adjusting for baseline age, sex and uACR (Table 3). Further adjustment with HbA_{1c} attenuated the associations between hyperfiltration and uACR at follow-up. In these adjusted models participants with age-adjusted hyperfiltration had a 60% ($p = 0.037$) higher uACR at follow-up, whereas, participants with mGFR ≥125 mL/min/1.73 m^2 had a 32% ($p = 0.080$) higher uACR at follow-up. Models with age-adjusted hyperfiltration explained a greater variance in follow-up uACR than models with the mGFR ≥125 mL/min/1.73 m^2 variable (Table 3). The relationship between hyperfiltration (using either definition) and uACR at follow-up was not significant with further adjustment for other covariates including waist-to-hip ratio, triglycerides, systolic blood pressure, anti-hypertensive medicine use and smoking. (Supplementary table 1). Though neither waist-to-hip ratio nor triglycerides remained significantly associated with uACR at follow-up after adjusting for baseline uACR or HbA_{1c} (data not shown).

Table 1
Baseline characteristics according to baseline albuminuria: the eGFR study.

	Normoalbuminuria	Albuminuria	All	p-value
N	234	173	407	
Age (years)	43 (14)	51 (13)	47 (14)	<0.001
Men, n (%)	88 (38)	68 (39)	156 (38)	0.81
uACR	0.8 (0.5, 1.4)	9.0 (4.8, 15.0)	2.0 (0.7, 16.7)	<0.001
Hyperfiltration groups				
Definition 1:				
mGFR < 90 mL/min/1.73 m^2, n(%)	54 (23)	85 (49)	139 (34)	<0.001
mGFR 90 to <125 mL/min/1.73 m^2, n(%)	131 (56)	60 (35)	191 (47)	
Hyperfiltration mGFR ≥125 mL/min/1.73 m^2, n(%)	49 (21)	28 (16)	77 (19)	
Definition 2:				
mGFR <90 mL/min/1.73 m^2, n(%)	54 (23)	84 (49)	138 (34)	<0.001
mGFR 90 to mGFR less than 10th percentile, n(%)	152 (65)	74 (43)	226 (56)	
Hyperfiltration mGFR 10th percentile for 10-yr age grps, n(%)	28 (12)	15 (9)	43 (11)	
mGFR (mL/min/1.73m^2)	107.3 (24.3)	99.3 (33.0)	99.8 (31.0)	<0.001
Diabetes status				
Normal glycaemia, n(%)	74 (76)	23 (24)	97 (24)	<0.001
Intermediate glycaemia, n(%)	94 (74)	33 (26)	127 (31)	
Diabetes, n(%)	66 (28)	117 (68)	183 (45)	
HbA_{1c} (mmol/mol)	45 (14)	60 (23)	51 (20)	<0.001
HbA_{1c} (%)	6.3 (1.3)	7.6 (2.1)	6.8 (1.8)	<0.001
Body Mass Index (kg/m^2)	30.2 (6.5)	30.9 (7.2)	30.5 (6.9)	0.29
Height (cm)	167 (9)	166 (8)	167 (8)	0.26
Waist circumference (cm)	100.6 (15.7)	104.5 (15.7)	102.3 (15.8)	0.0014
Waist-to-hip ratio	0.93 (0.08)	0.98 (0.10)	0.95 (0.09)	<0.001
Current smoking, n (%)	95 (41)	56 (33)	151 (38%)	0.059
Systolic blood pressure (mmHg)	114 (15)	123 (19)	118 (18)	<0.001
Diastolic blood pressure (mmHg)	73 (10)	76 (11)	75 (10)	0.006
Anti-hypertensive medicine use, n (%)	50 (21)	103 (60)	153 (38)	<0.001
Total cholesterol (mmol/L)	4.9 (1.0)	4.6 (1.1)	4.8 (1.0)	0.002
HDL cholesterol (mmol/L)	1.1 (0.4)	1.0 (0.3)	1.1 (0.3)	0.009
Triglycerides (mmol/L)	1.7 (1.2, 2.3)	2.1 (1.6, 2.9)	1.9 (1.3, 2.5)	<0.001
C-reactive protein (mg/L)	5.2 (3.0, 10.0)	5.7 (3.0, 12.0)	5.5 (3.0, 10.0)	0.22

Data are mean (SD) or median (25th, 75th percentile) unless otherwise specified. Diabetes defined as HbA_{1c} ≥ 48 mmol/mol (≥6.5%) or physician diagnosed, intermediate hyperglycaemia defined as HbA_{1c} ≥ 39 mmol/mol (5.7%) and <48 mmol/mol (6.5%) and normal glycaemia as HbA_{1c} < 39 mmol/mol (5.7%). Anti-hypertensive medicines included angiotensin converting enzyme inhibitors (ACEI) or angiotensin II receptor antagonists (ARB). uACR: urine albumin to creatinine ratio; mGFR: measured glomerular filtration rate; HbA_{1c}: haemoglobin A_{1c}; HDL: high density lipoprotein.

Table 2
Univariate associations of hyperfiltration and other risk factors measured at baseline with albuminuria at follow-up, stratified by baseline albuminuria status.

	Normoalbuminuria		Albuminuria	
	Beta-coefficient (95% CI)	p-value	Beta-coefficient	p-value
Age[a]	0.02 (0.01 to 0.03)	0.001	0.01 (−0.01 to 0.03)	0.225
Men	0.06 (−0.26 to 0.38)	0.724	0.08 (−0.49 to 0.65)	0.790
uACR[a] (mg/mmol)	0.76 (0.57 to 0.95)	<0.001	0.97 (0.85 to 1.10)	<0.001
Hyperfiltration groups[b]				
1. mGFR ≥ 125 mL/min/1.73 m^2	0.36 (−0.04 to 0.76)	0.076	0.05 (−0.75 to 0.86)	0.894
mGFR < 90 mL/min/1.73 m^2	0.30 (−0.08 to 0.69)	0.121	1.13 (0.53 to 1.72)	<0.001
2. 10th centile	0.71 (0.23 to 1.19)	0.004	0.91 (−0.08 to 1.89)	0.071
mGFR < 90 mL/min/1.73 m^2	0.32 (−0.06 to 0.69)	0.095	1.28 (0.72 to 1.83)	<0.001
Body Mass Index (kg/m^2)	0.02 (−0.003 to 0.04)	0.092	−0.02 (−0.06 to 0.02)	0.349
Height (cm)	−0.02 (−0.036 to 0)	0.056	−0.01 (−0.04 to 0.03)	0.709
Waist circumference (cm)	0.01 (0.001 to 0.02)	0.037	0.003 (−0.02 to 0.02)	0.781
Waist to hip ratio	2.86 (0.94 to 4.79)	0.004	4.44 (1.54 to 7.33)	0.003
Diabetes[c]	0.78 (0.39 to 1.17)	<0.001	1.09 (0.26 to 1.91)	0.010
Intermediate hyperglycaemia[c]	0.11 (−0.25 to 0.47)	0.550	0.63 (−0.35 to 1.61)	0.205
HbA_{1c} (mmol/mol)	0.02 (0.01 to 0.03)	<0.001	0.02 (0.004 to 0.03)	0.010
HbA_{1c} (%)	0.25 (0.14 to 0.37)	<0.001	0.18 (0.4 to 0.31)	0.010
Current smoking	−0.25 (−0.56 to 0.07)	0.127	0.32 (−0.28 to 0.92)	0.290
Systolic blood pressure (mmHg)	0.005 (−0.01 to 0.01)	0.356	0.01 (−0.001 to 0.03)	0.068
Diastolic blood pressure (mmHg)	−0.004 (−0.02 to 0.01)	0.625	0.01 (−0.02 to 0.04)	0.495
Anti-hypertensive medication use[d]	0.82 (0.45 to 1.18)	<0.001	0.72 (0.17 to 1.28)	0.011
Total cholesterol (mmol/L)	−0.12 (−0.28 to 0.03)	0.113	−0.12 (−0.39 to 0.14)	0.368
HDL cholesterol (mmol/L)	−0.43 (−0.85 to −0.01)	0.045	−0.56 (−1.52 to 0.40)	0.253
Triglycerides[a] (mmol/L)	0.33 (0.06 to 0.61)	0.017	1.01 (0.49 to 1.54)	<0.001

[a] Natural logarithm of variable.
[b] Hyperfiltration and mGFR < 90 mL/min/1.73 m^2 groups compared to those with mGFR ≥90 mL/min/1.73 m^2 and no hyperfiltration.
[c] Diabetes and intermediate hyperglycaemia compared to normal glycaemia.
[d] Anti-hypertensive medicines included angiotensin converting enzyme inhibitors (ACEI) or angiotensin II receptor antagonists (ARB).

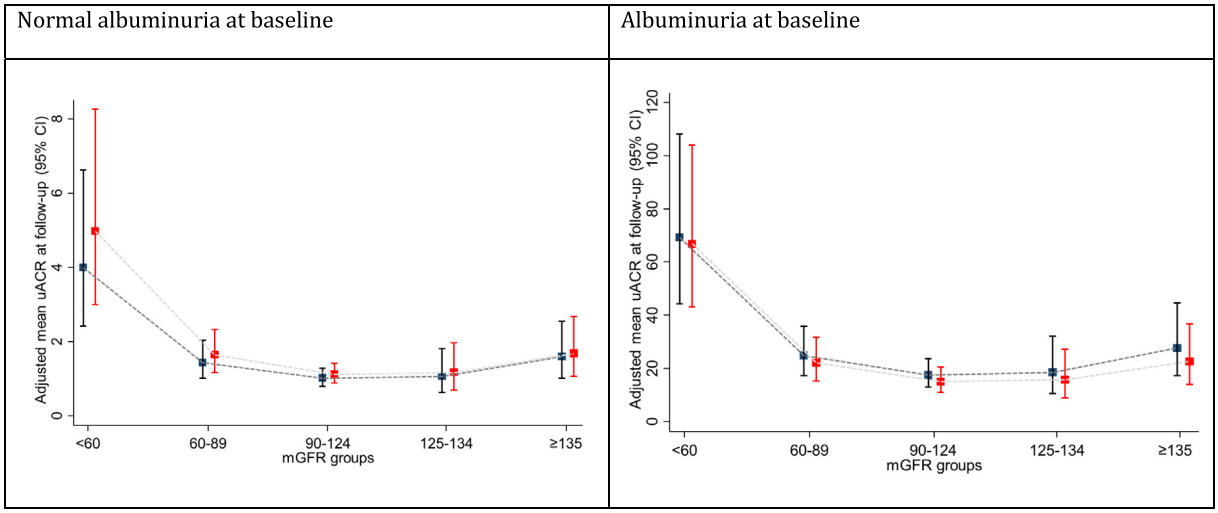

Fig. 1. Adjusted mean ACR at follow-up according to deciles of increasing baseline mGFR among those with and without albuminuria at baseline. Data are adjusted mean uACR (95% CI) at follow-up for mGFR groups determined from models A and B. The smoothed lines were obtained from a Lowess-based approach. Black = model A adjusted for age, gender, baseline urinary albumin to creatinine ratio; Red = model B adjusted for the variables in model A plus baseline HbA_{1c}. mGFR categorised according to clinical cut-points up to 90 mL/min/1.73 m^2 and then at 125 mL/min/1.73 m^2 and 135 mL/min/1.73 m^2, approximately corresponding to the 80th and 90th percentiles for mGFR.

The relationship between hyperfiltration and uACR at follow-up among those with albuminuria at baseline was largely modified by baseline uACR (Table 3). In this group, participants with mGFR <90 mL/min/1.73 m^2 had significantly higher uACR at follow-up in age- and sex- adjusted models, but these associations were explained by the confounding influences of baseline uACR and HbA_{1c}.

Baseline HbA_{1c} and uACR were significantly associated with uACR at follow-up in all models among those with and without albuminuria at baseline (data not shown). Models that included uACR and HbA_{1c} explained greater variation in uACR at follow-up than models with mGFR, age and gender (Table 3).

Similar findings were observed when models were also adjusted for baseline height, and if hyperfiltration was determined from absolute mGFR not corrected for body surface area (see Supplementary tables 2 and 3).

4. Discussion

Here we report on findings from the first study to assess whether hyperfiltration determined from directly measured GFR is associated with subsequently greater uACR level in Indigenous Australians who have a high prevalence of type 2 diabetes and kidney disease. This is an important study as while the relationship of hyperfiltration and development of albuminuria has been described in many studies enrolling individuals with type 1 diabetes,[22] there are few prospective studies of individuals with type 2 diabetes.[34] Over a median of three years, we observed a mild non-linear relationship between mGFR and uACR at follow-up. However, in adjusted models, the presence of hyperfiltration was more strongly associated with higher uACR at follow-up among those without, rather than among those with albuminuria at baseline. Additionally, we showed that hyperfiltration based on an age-adjusted definition, which took into consideration the age-related decline in GFR, was more strongly associated with higher uACR at follow-up than a definition based on a cut-point of 125 mL/min/1.73 m^2 irrespective of age. The associations observed between age-adjusted hyperfiltration and higher uACR at follow-up were also independent of uACR at baseline, but attenuated by baseline HbA_{1c}.

We demonstrated that in those with normoalbuminuria at baseline, presence of hyperfiltration defined using an age-adjusted definition at baseline was significantly associated with higher albuminuria at follow up. This finding supports the hypothesis that hyperfiltration may be a predictor of kidney disease progression before a patient presents with albuminuria. Indeed, in our study, hyperfiltration was not associated with higher albuminuria in those with albuminuria at baseline. Although a mGFR <90 mL/min/1.73 m^2 was significantly associated with higher uACR at follow-up in age and sex-adjusted models, further adjustment for baseline uACR attenuated this association indicating that those with pre existing albuminuria may already be on a pathway for albuminuria progression.[34]

The pathogenesis of hyperfiltration is complex, involving hemodynamic abnormalities and tubulo-glomerular feedback.[39,40] The hemodynamic hypothesis suggests that hyperfiltration is caused by changes in pre-glomerular (afferent) and post-glomerular (efferent) arteriolar tone as the result of an increase in a variety of vasoactive mediators induced by hyperglycaemia. Whereas, the tubular hypothesis proposes that hyperfiltration is initiated by hyperglycaemia through increased sodium reabsorption in the proximal tubule, which is mediated by the sodium-glucose cotransporter-2.[41] We showed that the association between age-adjusted hyperfiltration and uACR at follow-up among those with normoalbuminuria at baseline was associated with HbA_{1c}. Further adjustment for other important covariates such as blood pressure, smoking and waist-to-hip ratio did not appear to significantly impact on the relationship between hyperfiltration and uACR at follow-up. These findings support those by Ruggenenti et al.[42] who showed that persistent hyperfiltration over 6 months was a risk factor for the development of albuminuria in individuals with type 2 diabetes independent of other metabolic risk factors. This therefore implies that dysglycaemia driven hyperfiltration may be an important predictor of albuminuria progression, but that other metabolic abnormalities are also likely to be important mediators of hyperfiltration and its subsequent effects on CKD progression.

In the eGFR study cohort, we previously demonstrated that in Indigenous Australians hyperfiltration was also identified among those without type 2 diabetes.[28] We have now been able to extend these findings to show that hyperfiltration predicts higher uACR follow-up in those with diabetes and pre-diabetes. Others have also reported in prospective studies that pre-diabetes is significantly associated with the development of hyperfiltration and albuminuria.[43] This highlights that opportunities for prevention of CKD may exist in individuals before diabetes develops.

4.1. Strengths and limitations

A major strength of our study was the direct measurement of GFR at baseline to determine the presence of hyperfiltration in a relatively

Table 3
Adjusted associations of hyperfiltration with albuminuria at follow-up according to albuminuria at baseline.

	n	Normoalbuminuria			n	Albuminuria		
		Model 1 Adj age and sex	Model 2 Adj model 1 plus uACR	Model 3 Adj model 2 plus HbA_{1c}		Model 1 Adj age and sex	Model 2 Adj model 1 plus uACR	Model 3 Adj model 2 plus HbA_{1c}
mGFR ≥ 125	48	0.48 (0.09 to 0.88) 0.017	0.40 (0.03 to 0.76) 0.033	0.32 (−0.04 to 0.68) 0.080	27	−0.05 (−0.90 to 0.79) 0.901	−0.28 (−0.85 to 0.28) 0.327	−0.23 (−0.78 to 0.32) 0.417
Reference mGFR ≥ 90	130	–	–	–	58	–	–	–
mGFR < 90	53	0.04 (−0.36 to 0.45) 0.835	0.13 (−0.24 to 0.51) 0.478	0.13 (−0.23 to 0.50) 0.482	83	1.22 (0.55 to 1.90) <0.001	0.09 (−0.39 to 0.57) 0.712	0.25 (−0.23 to 0.73) 0.302
Adjusted R^2		0.0572	0.2156	0.2436		0.0681	0.5796	0.6053
10th centile mGFR	27	0.67 (0.18 to 1.16) 0.007	0.58 (0.14 to 1.02) 0.011	0.47 (0.03 to 0.92) 0.037	14	0.97 (−0.06 to 2.01) 0.065	0.60 (−0.10 to 1.30) 0.094	0.57 (−0.11 to 1.25) 0.098
Reference mGFR ≥ 90	151	–	–	–	72	–	–	–
mGFR < 90	53	0.07 (−0.34 to 0.48) 0.733	0.16 (−0.21 to 0.54) 0.388	0.15 (−0.21 to 0.52) 0.408	82	1.44 (0.78 to 2.11) <0.001	0.29 (−0.18 to 0.77) 0.228	0.44 (−0.03 to 0.91) 0.069
Adjusted R^2		0.0635	0.2223	0.2479		0.0902	0.5843	0.6104

mGFR: measured glomerular filtration rate; uACR: urine albumin-to-creatinine ratio: HbA_{1c}: haemoglobin A_{1c}; Hyperfiltration determined from mGFR (mL/min/1.73 m^2). Models on participants with complete data for all the variables included in the models (n = 231 for those without albuminuria and n = 168 with albuminuria ≥3 mg/mmol). uACR and HbA_{1c} remained significant in all multivariate models in those with and without albuminuria.

large sample of participants with and without albuminuria. With the exception of one large study,[23] other studies in individuals with type 2 diabetes reporting on hyperfiltration and development of albuminuria are either based on very small sample sizes using mGFR[24,25] or have used eGFR to define hyperfiltration.[26] Estimates of GFR are inaccurate in estimating mGFR in the hyperfiltration range because the creatinine based equations were derived from populations with CKD with relatively low mean measured GFR: 40 mL/min per 1.73 m^2 (SD, 21.2) for the development of Modification of Diet in Renal Disease (MDRD)[44] and 68 mL/min per 1.73 m^2 for Chronic Kidney Disease Epidemiology Collaboration CKDEPI (SD,40) equations respectively.[45] Furthermore, creatinine-based GFR estimates are influenced by filtration fraction and changes in tubular creatinine secretion in the setting of obesity, hyperglycemia, and hyperfiltration.[34] The following limitations should be considered when interpreting our findings. First, our study recruited a convenience study sample to ensure that participants had varying levels of diabetes and CKD, but this may have affected the representativeness of the study. Second, the study was undertaken in a range of clinical settings, including in remote health facilities, and as such we were not able to measure effective renal plasma flow.[46] Therefore, we were unable to identify participants who might have had single nephron hyperfiltration but normal or reduced global GFR. Third, ideally it would have been important to measure the effects of dopamine[47] and aminoacid infusion to determine the glomerular filtration reserve.[46] Fourth, due to the observational nature of our study design we were not able to assess the impact of medical treatment, in particular the use of blood pressure medication on our findings. Fifth, follow-up was short and only including a single assessment of mGFR which meant that it was not possible to assess the natural history of participants with hyperfiltration, and how their trajectories of mGFR might be associated with renal progression.

4.2. Future studies

Longer follow-up of this cohort will provide opportunities to assess whether stronger associations between hyperfiltration and development of albuminuria are observed in a sub-set of individuals with persistent hyperfiltration, as has been previously reported by Ruggenenti et al.[42] Furthermore, we were not able to assess the effects of sodium glucose co-transporters on uACR as these medications were not available for the majority of the participants at the time of this study. Empagliflozin has been shown to reduce hyperfiltration in individuals with type 1 diabetes,[48] and both empagliflozin and canagliflozin have been shown to improve renal outcomes in those with type 2 diabetes. Further studies assessing the renal effects of this medication class in Indigenous Australians who are at very high risk for developing kidney disease will be important.[49]

5. Conclusions

Hyperfiltration is not available for assessment in current clinical practice. However, our study shows that hyperfiltration is present in a significant proportion of Indigenous Australians without albuminuria and it is associated with higher uACR over a three year follow-up period. Importantly, hyperfiltration was identified in participants with both type 2 diabetes and intermediate hyperglycaemia and appears to be associated with other metabolic factors. Few studies have assessed the kidney disease implications of hyperfiltration in individuals across a spectrum of glycaemia. Our longitudinal research findings in Indigenous Australians, a population with rapidly progressive CKD, highlight that identification, management and follow-up of individuals with normoalbuminuria and hyperfiltration may be required to address the burden of kidney disease complications in this population.

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Authors contribution

All authors (Elif I Ekinci, Elizabeth LM Barr, Federica Barzi, Jaquelyne T Hughes, Paul D Lawton, Graham RD Jones, Wendy Hoy, Alan Cass, Mark Thomas, Ashim Sinha, George Jerums, Kerin O'Dea, Richard J MacIsaac, Louise J Maple-Brown) have contributed to:

1. Conception or design, or analysis and interpretation of data, or both:
2. Drafting the article or revising it.
3. Providing intellectual content of critical importance to the work described.
4. Final approval of the version to be published.

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Appendix A. Supplementary data

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