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Cross-sectional associations of albuminuria among Aboriginal and Torres Strait Islander adults: the eGFR Study

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Abstract

Objective: To describe the detailed associations of albuminuria among a contemporary cohort of Aboriginal and Torres Strait Islander people to inform strategies for chronic kidney disease prevention and management.

Methods: A cross-sectional analysis of Indigenous participants of the eGFR Study.

Measures: Clinical, biochemical and anthropometric measures were collected (including body-circumferences, blood pressure (BP); triglycerides, HbA1c, liver function tests, creatinine; urine- microscopic-haem, albumin: creatinine ratio (ACR), prescriptions- angiotensin converting enzyme inhibitor or angiotensin receptor II antagonist (ACEI/ARB). Albuminuria and diabetes were defined by an ACR>3.0 mg/mmol, and HbA1c≥48 mmol/mol or prior history respectively. Waist: hip ratio (WHR), and estimated glomerular filtration rate (eGFR) were calculated. ACR was non-normally distributed; a logarithmic transformation was applied (in base 2), with each unit increase in log2-albuminuria representing a doubling of ACR.

Results: 591 participants were assessed (71% Aboriginal, 61.6% female, mean age 45.1 years, BMI 30.2 kg/m^2, WHR 0.94, eGFR 99.2 ml/min/1.73m^2). The overall prevalence of albuminuria, diabetes, microscopic-haem and ACEI/ARB use was 41.5%, 41.5%, 17.8% and 34.7% respectively; 69.3% of adults with albuminuria and diabetes received an ACEI/ARB. Using multivariable linear regression modelling, the potentially modifiable factors independently associated with log2-albuminuria were microscopic-haem, diabetes, WHR, systolic BP, alkaline phosphatase (all positive) and eGFR (inverse).

Conclusion: Albuminuria is associated with diabetes, central obesity and haematuria. High ACEI/ARB prescribing for adults with diabetes and albuminuria was observed. Further understanding of the links between fat deposition, haematuria and albuminuria is required.

Introduction

Albuminuria is an indicator of microvascular injury[1], the metabolic syndrome, diabetic and non-diabetic chronic kidney disease (CKD) and excess cardiovascular disease mortality[2-4]. Guidelines have recently recommended CKD screening and staging using both albuminuria and estimated glomerular filtration rate (eGFR)[2]. Local and national clinical management guidelines for CKD also recommend renoprotective medication use[5, 6].

Albuminuria without impaired GFR[7], or which precedes diabetes is a common CKD presentation in Aboriginal and Torres Strait Islander (TSI) people of northern Australia. In this population, albuminuria has been linked with overweight, dialysis dependent end stage kidney disease (ESKD) and mortality[8, 9]. Understanding the associations of albuminuria among Aboriginal and Torres Strait Islander people, such as the consistency of clinical prescribing practices for adults with CKD, may highlight health system and broader health promotion measures for ESKD prevention. Our aim was to describe the clinical, anthropometric and biochemical associations of albuminuria among volunteering Aboriginal and Torres Strait Islander adults within different levels of kidney function living across large regions of northern and Central Australia.

Methods

Participants

The life expectancy gap attributed to adult chronic diseases has contributed to a younger median age of Indigenous Australians than other Australians (21 v 37 years)[10]. As such, annual health assessments are recommended for Indigenous Australian adults (from the age of fifteen)[11]. Reflecting the different age structures and risks associated with chronic disease, participants in the eGFR Study were self-identifying Aboriginal and Torres Strait Islander people (Indigenous Australians) aged at least 16 years[12]. With the exception of adults undertaking dialysis, who had rapidly changing kidney function or were pregnant or breastfeeding, all adults

expressing interest to participate were able to be stratified for inclusion, including those with diabetes or existing kidney disease. Recruitment areas focussed on regions with a high incidence of ESKD[13], including more than 20 sites in the Northern Territory, Central Australia, Thursday Island and Far North Queensland, and the Kimberley and Goldfield regions of Western Australia. Although Aboriginal and Torres Strait Islander peoples are both recognised as Indigenous peoples of Australia, there are several unique features including population origins (Micronesia v Melanesia origins), cultural practises[14] and patterns of dyslipidaemia[15]. Torres Strait Islander peoples are also a minority group within the Indigenous Australian population[16], however it was not the goal of the eGFR Study to recruit equal numbers of TSI and Aboriginal participants. Participants provided informed consent. Ethics approval was provided by the Northern Territory Department of Health and Families and Menzies School of Health Research Human Research Ethics Committee, including the Indigenous ethics subcommittee, which has the power of veto over studies involving Indigenous Australian peoples; Cairns and Hinterland Health Services District Human Research Ethics Committee; Central Australian Human Research Ethics Committee; Western Australian Aboriginal Health Information and Ethics Committee; Royal Perth Hospital Ethics Committee.

Measures

Diabetes was defined by HbA1c≥48 mmol/mol[17] or physician diagnosis or by current use of anti-diabetic medications. Hypertension was defined by physician diagnosis, current use of anti-hypertensive medications or BP≥140/90 mmHg[18]. Blood pressure was described as the mean of three resting blood pressure measurements (taken at least 3 minutes apart) after the participant had been seated quietly for at least 5 minutes using an automated sphygmomanometer as previously described[12]. Current smoking was self-reported. Smoking duration in years was calculated in current smokers. Alcohol excess was recorded if participants recorded no alcohol free-days[19] or >20 units consumed per week. Remoteness index of usual residence was calculated by Accessibility Remoteness Index of Australia with scores >10.53

indicating residence in a community/ town in very remote Australia[20]. Urine dipstick was used as a screening test to evaluate for the presence of chronic kidney disease[21]. Urine samples were sent for urine culture if urine dipstick was positive for either of nitrites, leucocytes or haem. We describe microscopic-haem as the presence of at least trace haem on urine dipstick, in the absence of bacteriuria defined by the presence of a single bacterial colony count of $\geq 10^5$/ml. In this analysis, bacteriuria is not urinary tract infection. Medication prescriptions for aspirin, HMG-CoA enzyme reductase inhibitors (statins), non-steroidal anti-inflammatory drugs (NSAID's), antihypertensive medications including angiotensin converting enzyme inhibitors (ACEI) and angiotensin II receptor antagonists (ARB) were confirmed by the medical record. ACEI/ARB described the prescription with either an ACEI or ARB. Measurements of resting blood pressure, height, weight, waist and hip circumferences and bioimpedance were collected; waist to hip ratio (WHR), body mass index (BMI) and fat-free mass percent (FFM%)[22] were calculated. An optimal FFM% range for healthy middle-aged adults (40-59 years) with BMI 18-25 kg/m^2 in males (79-89%) and females (65-76%) has been previously described[23].

Laboratories local to each recruitment site measured non-fasting serum high density lipoprotein (HDL)-cholesterol, glycated haemoglobin (HbA1c), liver function tests and urine albumin to creatinine ratio (ACR). Detailed methods at each laboratory for these measures have been previously described[12], and each pathology laboratory was accredited by NATA (National Association of Testing Authorities, Australia). Albuminuria was defined as an ACR>3.0 mg/mmol[2]. Serum creatinine was measured centrally using an IDMS standardised enzymatic assay[24], and estimated GFR (eGFR) was calculated by the CKD-EPI formulae without use of the correction for African Americans[24].

Six hundred and fifty three Indigenous Australian participants were assessed at the baseline eGFR Study. This analysis describes adult participants defined as at least

18 years, since creatinine-derived variables (eGFR) are not validated in populations younger than 18 years. Thus this analysis describes 591 participants accounting for the following exclusions: age<18 years (n=10); missing data for urine ACR (n=46); presence of bacteriuria confirmed by urine culture (n=6).

Statistical Analyses

Descriptive characteristics of participants were reported by Indigenous status (Aboriginal or TSI) and, within each indigenous group, separately for those without and with albuminuria. Categorical variables were described with a percentage and continuous variables, when normally distributed, with mean and standard deviation. Continuous variables with a right skewed distribution were log transformed when possible, otherwise were described with median and interquartile range. P values were derived to test differences in distribution of participants' characteristics between those with and without albuminuria using Chi-squared test for categorical factors and Students t-test for normally distributed continuous factors. The Wilcoxon rank-sum test was used to compare medians in not normally distributed variables.

The outcome of ACR displayed a highly right skewed distribution, thus a logarithmic transformation in base 2 (log2-albuminuria) was carried out to normalise the distribution. Therefore each unit rise in log2-albuminuria represents a doubling in ACR.

As the cohort had a higher proportion of females, and aging is associated with chronic disease and adiposity, we used linear regression models, adjusted for age and gender in each indigenous group to examine the effect each variable had on log2-albuminuria, and identify which variables had different coefficient loadings between indigenous groups. A multivariable linear regression analysis was then used to examine the associations between participants' characteristics and the outcome, log2-albuminuria. The initial model was built with gender, ethnicity and age, and all other predictor variables identified on linear modelling with $p<0.10$.

Using a stepwise backwards process, the final significant model was obtained by removing one variable at a time if its main effect in the model was $p>0.05$, until all remaining variables were significantly associated with the outcome ($p<0.05$). We assessed and did not observe an interaction between indigenous ethnicity and the other covariates. Collinearity between predictor variables was assessed using the variance of inflation factor, a maximum value of 10 being deemed acceptable. To enhance the clinical interpretation, we subsequently converted the equation from log2-albuminuria to ACR as the outcome variable, in order to demonstrate the contribution (as percent additive contribution) of each independent variable with estimated ACR (in mg/mmol). Statistical analyses were performed using Stata v14 (Stata Corporation, College Station, TX).

Results

Albuminuria, diabetes, hypertension and overweight were key findings observed among the 591 participants (Table 1). The median (IQR) ACR in Aboriginal and TSI participants was 2.5 (0.7, 30.4) and 1.1 (0.6, 4.6) mg/mmol respectively ($p<0.001$). A higher proportion of older participants (>60 years) and Aboriginal participants had albuminuria and low eGFR (<60 ml/min/1.73m^2) (Table 2). Microscopic-haem was observed in 17.8% of participants overall, including in adults with and without albuminuria (23.9%, 13.5%, $p=0.002$). A wide range in FFM% was observed in participants (49-94%), though FFM% overall was lower in Aboriginal than TSI participants (Aboriginal, mean (SD): 64.9 (9.7) % v TSI: mean (SD): 66.9 (9.4) %, $p=0.03$). As expected, FFM% was higher in males than females (74 (8.3) v 60.3 (6.0) %, $p<0.001$). ACEI/ARB's were the most commonly prescribed class of antihypertensive medications (Table 3). The highest frequency of medication prescription for ACEI/ARB, statins and aspirin was observed in adults with albuminuria who also had diabetes (Figure 1).

Characteristics of participants with albuminuria (ACR>3.0 mg/mmol) included older age, diabetes, hypertension, abdominal obesity, use of ACEI/ARB and statins, higher

values each of systolic and diastolic blood pressure, HbA1c and alkaline phosphatase, and lower eGFR (Table 3). Albuminuria was also associated with higher WHR (without a comparably higher value in BMI or weight) in Aboriginal male and female participants. In contrast, TSI males with albuminuria had a larger body size marked by higher adiposity (indicated by higher weight, higher BMI and lower FFM%) in addition to higher WHR than TSI males with normoalbuminuria. By comparison (and unlike Aboriginal females), albuminuria in TSI females was not significantly associated with WHR (Table 3).

Bivariate analysis showed significant associations between log2-albuminuria and WHR (r=0.34) and serum GGT (r=0.19) respectively. GGT was also positively associated with WHR (r=0.26), ALP (r=0.40) and diabetes (35 v 29 U/L, p=0.017). Bilirubin was inversely associated with ALP (r= -0.19). High serum GGT (>50 U/L) was observed in 31% of participants, though reporting of excess alcohol consumption was low in participants (n=49, 8.3%).

Linear Regression modelling adjusted for age and gender

Log2-albuminuria when adjusted for age and gender, was independently associated with the following variables in all participants ($p \leq 0.001$): microscopic-haem, diabetes, WHR, total cholesterol, aspirin use, statin use, ACEI/ARB use, hypertension, systolic BP, diastolic BP, HbA1c, HDL-cholesterol, alkaline phosphatase, GGT, triglycerides, (all positive) and eGFR (inverse) and bilirubin (inverse); and at the level of $p<0.10$ as follows: waist (p=0.06) and total protein (p=0.07). Differences in the coefficient loading between Indigenous groups (beta coefficient, Aboriginal, TSI) were noted respectively for: diabetes (2.54, 1.46), microscopic-haem (2.0, 1.0), WHR (8.12, 7.40), aspirin use (1.87, 0.92) and total cholesterol (-0.37, -0.13).

Log2-albuminuria when adjusted for age and gender, was not linearly associated in the aggregate group with: height (p=0.10), alanine transferase (p=0.14), remoteness index (p=0.16), HDL: total cholesterol ratio (p=0.21), FFM% (p=0.32), current

smoking (p=0.56), NSAID use (p=0.72), weight (p=0.74) and body mass index (p=0.94).

In the multivariable linear regression model in all participants (Table 4), 56% of the variance in log2-albuminuria was explained by Aboriginal ethnicity, female sex, WHR, systolic blood pressure, diabetes, ACEI/ARB use, ALP and microscopic-haem (all were positive associations), and lower eGFR. ACEI/ARB use explained 2.2% of the 56% variance in log2-albuminuria among all participants. Table 5 shows the contribution of each independent variable with estimated ACR (as an untransformed variable in mg/mmol). For example, using the simulated patients, with all measures being equal, diabetes explained an additive 186% higher estimated ACR than the value observed in participants without diabetes (patient 6 v 5: ACR 13 mg/mmol v 5 mg/mmol).

Discussion

We examined the cross-sectional associations of albuminuria among 591 Indigenous Australian adults of the eGFR Study, who were recruited across multiple northern and Central Australian sites and had fulfilled the pre-defined recruitment criteria of good health, increased cardio-metabolic risk or CKD. Of the ten factors identified in the multivariable linear regression model, the categorical factors strongly associated with estimated ACR as potential targets of disease prevention and mitigation were diabetes and microscopic-haem. Furthermore systolic blood pressure, lower eGFR and higher WHR were the continuous variables which were most strongly associated with estimated ACR. Other key findings of this analysis included the strong association of albuminuria with features of the metabolic syndrome among participants; the co-existence of microscopic-haem in a population with a high frequency of diabetes; and the high prescription rates of renoprotective agents among adults with co-existing cardio-metabolic risks including diabetes, hypertension and albuminuria.

Albuminuria, ALP, GGT and central and total adiposity

Alkaline phosphatase, GGT, uric acid and albuminuria are all biochemical markers associated with the metabolic syndrome[25-27]. GGT and ALP are both correlated with abdominal adiposity[27] and GGT can indirectly predict ultrasound-proven hepatic steatosis[28], a condition within the metabolic syndrome spectrum. In one remote Aboriginal community, it was previously reported that albuminuria was positively associated with several cardio-metabolic disease risk markers: blood pressure, uric acid, diabetes, CRP and serum GGT ($p=0.05$)[29]. Additionally, comparable decreases in GGT concentrations over time were associated with lower waist circumference among Indigenous adults of north Queensland[30]. We suggest hepatic steatosis is likely among Aboriginal participants when overweight, given the positive association of GGT and ALP with WHR and log2-albuminuria in our study. This may result from a low threshold for hepatic lipid storage resulting in preferential central adiposity that accompanies elevated fasting insulin concentrations. It is proposed that these elevated insulin concentrations are to historically mitigate periods of recurrent relative low food intake[31]. A low threshold for hepatic lipid storage may also be consequent to limited peripheral adipose storage depots, due to a lower absolute lean mass.

Log2-albuminuria was strongly associated with WHR in the multivariate regression model, which is an observation consistent among Aboriginal people across northern and Western Australia[32]. Among Aboriginal participants, this central fat distribution (at comparably lower BMI than TSI participants) is likely to be a progression of the physique described by Piers et al. who reported a higher WHR, and percent fat adjusted for BMI in healthy Aboriginal young adults relative to Caucasian participants[33].

In this analysis, overweight was a common feature of participants, indicated by high WHR, BMI and low FFM%. These low FFM% values were comparable to previous reported values in Aboriginal adults of similar age and BMI[34, 35]. Consistent with

other studies, we report a higher FFM% in TSI than Aboriginal participants[36]. We note adults with higher (than lower) FFM% have an enhanced capacity for insulin secretion[37]. This might suggest TSI groups have an optimised capacity for insulin clearance across a larger weight-range due to a higher proportion of lean mass than Aboriginal people[36], and is consistent with the lack of association of log2-albuminuria with FFM% in participants in this analysis.

Central obesity (than total obesity) was previously reported to be more strongly associated with cardio-metabolic risk across multi-ethnic populations[38]. Likewise, we show that albuminuria is associated with WHR and ALP (and not with FFM%). WHR in combination with ALP may have better defined the physical attributes related to the metabolic syndrome of each indigenous group. The Aboriginal ethnicity covariate may have further explained the difference in body fat distribution between groups.

Microscopic haem

Albuminuria was observed in participants with and without diabetes and with and without microscopic-haem as detected by urine dipstick. This association is consistent with the leading clinical diagnoses of Indigenous Australians with ESKD[39], and also consistent with the mixed and overlapping renal pathologies in biopsy series of remote living Aboriginal people with diabetes[40]. One remote Aboriginal community with a high risk of ESKD had documented haematuria amongst 25% of adults[41]. A greater understanding of the pathogenic impact of microscopic-haem in diabetic and non-diabetic CKD in both Indigenous groups is needed.

Renin-Angiotensin system blockade

As in other populations, angiotensin converting enzyme inhibitors have demonstrated renoprotective effects in Aboriginal Australians[42, 43], and are the cornerstone of medical treatment guidelines for adults with CKD[5]. The use of an ACEI/ARB is in large part a treatment decision for cardio-metabolic risk modification

related to albuminuria, diabetes, and hypertension. The extent to its use may vary according to the health service provider awareness and vigour. In this analysis, there was high alignment with guidelines for ACEI/ARB prescribing for adults with diabetes, which were often co-prescribed with statins and aspirin. The majority of albuminuric participants without diabetes had micro-albuminuria (ACR 3-30 mg/mmol) and preserved eGFR. In this group ACEI/ARB prescribing practices were again consistent with local and national guidelines, since their use is not recommended for normotensive, non-diabetic adults with micro-albuminuria and preserved eGFR[5, 6]. This cross-sectional analysis reports the positive association of ACEI/ARB use with albuminuria. We suggest ACEI/ARB are beneficial agents, and the model identifies they are being used substantially for the treatment of albuminuria or conditions associated with albuminuria (including diabetes and hypertension). The lower frequency of current smokers in adults with albuminuria suggests participants' engagement in health education strategies.

Several key strengths of this study suggest generalisability of our findings. We assessed a large cohort, involving sites across five major Australian regions, and included participants with a wide range of eGFR, and used measures validated in Indigenous Australians (FFM%, eGFR). We have highlighted the key modifiable factors associated with albuminuria in Indigenous Australians, and the between-group differences of albuminuria in this population, which is relevant in informing health intervention strategies. Some limitations are acknowledged; the study was not intended to be population representative, and our findings may be subject to volunteer bias thereby limiting generalisability. We recruited 653 Indigenous participants in the eGFR study, and the 62 participants who were excluded from this analysis (due to missing ACR values, young age or bacteriuria) were younger and had a lower WHR. Furthermore, the final multivariable regression model describes 517/591 participants with complete data for all 10 variables. The serum alkaline phosphatase concentration was higher in participants included in the final model, which may affect the strength of association of the factors with log2-albuminuria. In

this analysis the description of microscopic-haem was based on urine dipstick rather than the gold standard measure defined as microscopic urinary red blood cells ≥3-5/HPC on centrifuged urine. Albuminuria and microscopic-haem were measured once, thus misclassification was possible, but minimised by independent medical record review. It was not possible to distinguish microscopic-haem as glomerular or lower urinary tract origin, or explore the association of albuminuria with diet, weight trajectory or other lifestyle factors.

Conclusions

We report a strong cross-sectional association of log2-albuminuria with abdominal obesity, diabetes and microscopic-haem among Indigenous Australian participants who are relatively younger than other populations with chronic kidney disease. There was also high ACEI/ARB use in adults with diabetes and albuminuria. Although the mechanisms linking albuminuria, abdominal obesity and fatty liver remain to be elucidated, these associations were striking in participants. Further understanding of the links between fat deposition, haematuria and albuminuria is required, in order to strengthen the public health strategies for obesity, diabetes and CKD.

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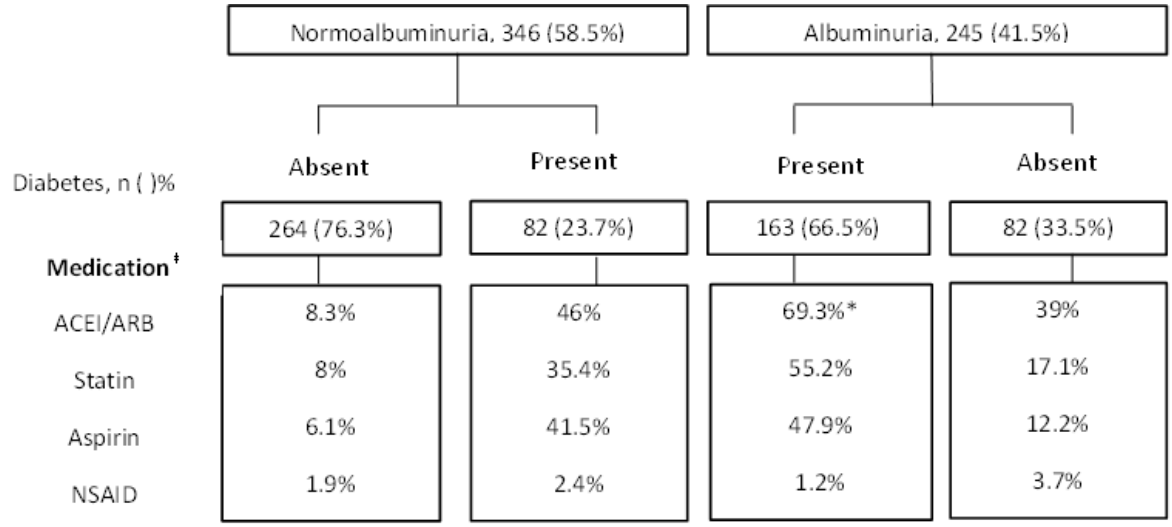

n=591 participants. ‡ Denominator for medication data is number in respective diabetes present/ absent column.

*ACEI/ARB use overall was 69.3% (prevalent diabetes 74%, incident diabetes 26%).

Figure 1: Medication prescription among participants by albuminuria and diabetes

Table 1: Participant characteristics

	n (%)
Aboriginal Ethnicity	419 (70.9%)
Female sex	364 (61.6%)
Usual residence: very remote	344 (59.6%)
Diabetes	245 (41.5%)
Hypertension	255 (43.1%)
Albuminuria ǂ	245 (41.5%)
New Case	122 (49.8%)
Prevalent Case	100 (40.8%)
Haematuria ǂǂ	99 (17.8%)
eGFR<60 ml/min/1.73m^2 ǂǂ	103 (17.5%)
BMI >25 km/m^2	450 (76.6%)
	Mean (standard deviation)
Age, years	45.1 (14.6)
eGFR⌈, ml/min/1.73m^2 ǂǂ	99.2 (79.8-112.3)
ACR⌈, mg/mmol	1.9 (0.7-17.3)
HbA1c, mmol/mol	50 (19.6)
Systolic BP, mmHg	118 (18)
Diastolic BP, mmHg	75 (10)
BMI, kg/m^2	30.2 (7.2)
FFM % males	64.4 (11.4)
FFM % females	48.1 (9.0)
WHR males	0.98 (0.09)
WHR females	0.92 (0.08)

Data are number (%) or mean (SD) or ⌈median (interquartile range). n=591. ǂǂIncomplete data as follows: usual residence category (577), haematuria (556), eGFR (589), HbA1c (575), blood pressure (582), BMI (587), FFM% (524), WHR (560). ǂUnable to categorise albuminuria as incident or prevalent in n=23/245 (9.4%) participants. Abdominal obesity is defined by WHR>0.90 in males and >0.85 in females and/or BMI>30kg/m^2 [26]

Table 2: The distribution of participants by female gender, albuminuria and low eGFR, and by indigenous ethnicity, age and BMI

		Indigenous group			Age (years)			Body Mass Index (kg/m^2)		
	n	TSI n=172	Aboriginal n=418	p	<60 n=492	≥60 n=99	p	<25 n=137	≥25 n=450	p
Female	N=364	58.7%	62.8%	0.36	61.3%	62.6%	0.81	51.1%	64.9%	0.004
Albuminuria	N=245	27.9%	47%	<0.001	36.6%	65.7%	<0.001	42.3%	40.9%	0.76
eGFR<60 ml/min/1.73m^2	N=103	12.3%	19.6%	0.03	11.6%	46.5%	<0.001	22.6%	15.6%	0.058

Total participants are n=591; data are incomplete: BMI (n=587), eGFR (n=589)

Table 3: Descriptive characteristics participants without and with albuminuria, by ethnicity and gender

		Aboriginal						Torres Strait Islander					
		Female			Males			Females			Males		
	n	Normo-albuminuria N=141	Albuminuria N=122	P value	Normo-albuminuria N=81	Albuminuria N=75	P value	Normo-albuminuria N=70	Albuminuria N=31	P value	Normo-albuminuria N=54	Albuminuria N=17	P value
n(%)													
Very remote residence	577	69 (50.4)	58 (48.7)	0.795	45 (55.6)	35 (48)	0.345	60 (87.0)	23 (74.2)	0.116	41 (80.4)	13 (81.3)	0.940
Diabetes	591	34 (24.1)	84 (68.9)	<0.001	15 (18.5)	49 (65.3)	<0.001	20 (28.6)	19 (61.3)	0.002	13 (24.1)	11 (64.7)	0.002
Hypertension	585	40 (28.4)	85 (69.7)	<0.001	18 (22.2)	50 (66.6)	<0.001	19 (27.1)	16 (51.6)	0.017	17 (31.5)	10 (58.8)	0.043
Current smoking	580	64 (46.4)	39 (32.8)	0.026	42 (51.9)	32 (43.2)	0.284	27 (38.6)	7 (23.3)	0.140	25 (48.1)	3 (18.8)	0.037
Microscopic-haem	556	24 (17.9)	30 (26.3)	0.110	2 (2.8)	15 (20.8)	0.001	12 (18.2)	7 (25.9)	0.400	6 (11.8)	3 (17.7)	0.535
Medication Prescription													
Any BP medication	591	28 (19.5)	75 (61.4)	<0.001	14 (17.3)	49 (65.3)	<0.001	12 (17.1)	19 (61.3)	<0.001	11 (20.4)	9 (52.9)	0.009
ACEI/ARB	591	26 (18.4)	73 (59.8)	<0.001	14 (17.3)	45 (60.0)	<0.001	10 (14.3)	18 (58.1)	<0.001	10 (18.5)	9 (52.9)	0.005
Statin	591	23 (16.3)	49 (40.2)	<0.001	7 (8.6)	33 (44.0)	<0.001	11 (15.7)	14 (45.2)	0.002	9 (16.7)	8 (47.1)	0.010
Aspirin	591	18 (12.8)	36 (29.5)	0.001	9 (11.1)	34 (45.3)	<0.001	14 (20)	12 (38.7)	0.047	9 (16.7)	6 (35.3)	0.101
NSAID	591	2 (1.4)	2 (1.6)	0.884	2 (2.5)	1 (1.3)	0.606	1 (1.4)	0 (0)	0.504	2 (3.7)	2 (11.8)	0.209
Mean (Standard deviation)													
Age (years)	591	42.0 (13.5)	51.0 (13.6)	<0.001	37.9 (13.3)	50.8 (13.9)	<0.001	42.7 (13.7)	49.3 (14.7)	0.033	40.7 (15.8)	52.4 (10.5)	0.006
Height (cm)	587	163.1 (7.2)	161.7 (6.1)	0.086	172.5 (5.3)	172.0 (6.7)	0.001	161.9 (5.8)	161.6 (5.0)	0.82	173.6 (6.4)	173.9 (6.0)	0.88
Weight (kg)	589	79.9 (19.2)	78.9 (19.5)	0.68	83.2 (20.2)	86.3 (21.8)	0.35	84.5 (19.5)	91.3 (21.2)	0.12	93.0 (24.8)	108.6 (18.7)	0.02
BMI	587	29.9 (6.5)	30.2 (7.3)	0.78	26.9 (6.1)	29.0 (6.8)	0.046	32.2 (6.8)	35.0 (8.0)	0.073	30.8 (8.0)	35.8 (5.3)	0.02
Waist (cm)	564	99.6 (14.7)	102.6 (15.9)	0.13	96.0 (17.8)	104.0 (15.5)	0.003	100.0 (15.6)	104.3 (13.8)	0.20	100.8 (18.5)	117.0 (12.2)	0.002
Waist-hip ratio	560	0.91 (0.08)	0.95 (0.09)	0.001	0.95 (0.10)	1.03 (0.08)	<0.001	0.88 (0.07)	0.91 (0.09)	0.241	0.94 (0.08)	1.03 (0.05)	<0.001
Fat free mass (%)	524	60.1 (5.9)	59.5 (5.8)	0.38	75.1 (7.9)	72.8 (8.7)	0.12	61.8 (6.5)	61.5 (6.2)	0.85	75.2 (8.9)	70.2 (3.7)	0.034
SBP (mmHg)	582	113 (15)	124 (20)	<0.001	117 (14)	127 (21)	0.001	109 (15)	122 (4)	0.001	117 (15)	129 (16)	0.013
DBP (mmHg)	582	74 (10)	77 (10)	0.026	74 (10)	78 (12)	0.044	69 (8)	75 (9)	0.002	73 (10)	79 (12)	0.03
HbA1c (mmol/mol)	575	45.1 (15.4)	56.8 (21.2)	<0.001	42.1 (8.6)	59.3 (23.2)	<0.001	45.6 (18.7)	59.9 (24.8)	0.003	42.5 (11.7)	66.5 (28.4)	<0.001
Total Cholesterol (mmol/L)	571	4.9 (1.2)	4.5 (1.0)	0.002	5.0 (1.0)	4.5 (1.0)	0.003	5.0 (0.9)	5.2 (1.2)	0.357	5.1 (0.9)	4.7 (1.0)	0.162

HDL-Cholesterol (mmol/L)	556	1.14 (0.37)	1.08 (0.31)	0.14	1.10 (0.31)	1.00 (0.30)	0.047	1.16 (0.35)	1.02 (0.23)	0.076	1.07 (0.34)	0.86 (0.17)	0.025
Total Cholesterol/HDL ratio	557	4.7 (1.6)	4.5 (1.3)	0.24	4.8 (1.4)	4.8 (1.7)	0.99	4.6 (1.4)	5.3 (1.3)	0.037	5.2 (1.6)	5.6 (1.2)	0.29
Total Protein (g/L)	585	78 (11)	81 (11)	0.068	76 (17)	78 (12)	0.43	73 (4)	73 (6)	0.99	73 (16)	72 (19)	0.82
Alkaline phosphate (U/L)	579	105(32)	131(42)	<0.001	98 (29)	114(35)	0.003	77 (20)	91 (18)	0.001	81(23)	89(24)	0.27
Alanine Transferase (U/L)	583	26 (14)	28 (18)	0.30	35 (20)	34 (26)	0.90	27 (14)	29 (18)	0.56	36 (19)	30 (14)	0.26
Median (interquartile range)													
Cigarettes (per day*)	580	10 (6.5, 20)	12 (5.5, 20)	0.84	15 (6, 25)	13.5 (5.5, 25)	0.62	10 (4, 17)	8 (6, 25)	0.37	8 (5, 15)	4 (3, 25)	0.60
Smoking duration (years)*	559	19 (10, 28)	22 (15, 33)	0.05	17.5 (11, 25)	26 (18, 35)	0.006	16 (10, 21)	12 (8, 29.6)	0.56	14 (6, 28)	34 (25, 48.5)	0.09
Creatinine (µmol/L)	584	58 (53, 68)	70 (56, 125)	<0.001	81 (71, 90)	95.5 (74, 159)	<0.001	60 (54, 64)	64.5 (57, 98)	0.021	88 (79, 93)	108 (78, 140)	0.052
eGFR (ml/min/1.73 m^2)	584	105 (93, 116)	90 (39, 108)	<0.001	106 (93, 115)	84 (38, 105)	<0.001	105 (96, 116)	95 (57, 112)	0.01	98 (84, 110)	69.5 (49, 101)	0.003
γ glutamyl transferase (U/L)	585	32 (25, 52)	41 (28, 75)	0.007	47 (28, 77)	57 (30, 89)	0.09	21 (16, 28)	25 (19, 34)	0.10	29 (22, 40)	25 (19, 35)	0.22
Geometric Mean (95% Confidence interval)													
Triglycerides (mmol/L)	571	1.77 (1.63, 1.92)	2.06 (1.88, 2.25)	0.015	1.79 (1.59, 2.02)	2.41 (2.11, 2.76)	0.003	1.36 (1.18, 1.56)	1.73 (1.45, 2.07)	0.054	1.56 (1.32, 1.85)	2.16 (1.73, 2.70)	0.057
Bilirubin (µmol/L)	579	5.4 (5.0, 5.8)	4.8 (4.4, 5.2)	0.038	7.2 (6.6, 7.9)	5.9 (5.2, 6.7)	0.14	8.9 (8.2, 9.7)	7.7 (6.7, 8.9)	0.084	10.7 (9.7, 11.9)	9.8 (8.5, 11.4)	0.41

** For current smokers*

Table 4: Multivariable linear regression model of log2-albuminuria in all participants

	B Coefficient	95% Confidence Interval		p
Aboriginal ethnicity	0.53	0.09	0.97	**0.017**
Age (years)	-0.02	-0.04	-0.01	**0.012**
Female	0.20	-0.23	0.62	0.359
Microscopic-haem	1.30	0.81	1.79	**<0.001**
Diabetes	1.52	1.06	1.98	**<0.001**
Use of ACEI /ARB	1.24	0.77	1.71	**<0.001**
Systolic BP (mmHg)	0.03	0.02	0.04	**<0.001**
eGFR (ml/min/1.73m^2)	-0.04	-0.05	-0.03	**<0.001**
WHR	2.75	0.25	5.26	**0.032**
Alkaline phosphatase (U/L)	0.01	0.003	0.015	**0.001**
Constant	-2.99	-5.80	-0.18	**0.037**
		Model R^2 0.56; n=517		

Variables in the initial model were selected if they were linearly associated with log2-albuminuria (adjusted for age and gender) in all participants with a p value <0.10 as follows: microscopic-haem, diabetes, hypertension, ACEI/ARB use, statin use, aspirin use, systolic blood pressure (BP), diastolic BP, eGFR, HbA1c, triglycerides, total cholesterol, HDL-cholesterol, waist, WHR, serum total bilirubin, alkaline phosphatase (ALP), gamma glutamyl transferase, total protein. Age, gender and indigenous ethnicity (Aboriginal =1, TSI=0) were forced in the model. Categorical variables were coded 1=present, 0=absent; continuous variables were included in equation in 1 unit increments.

Log2-albuminuria was converted to ACR (in mg/mmol) using $ACR=\exp^{(\text{equation x } \log_2)}$. Thus ACR (mg/mmol) is represented as follows:

$$ACR= \exp^{[(0.53(\text{if Aboriginal}) -0.02 (\text{age}) + 0.20 (\text{if female}) + 1.30 (\text{if microscopic- haem}) + 1.52 (\text{if diabetes}) + 1.24 (\text{if ACEI/ARB use}) + 0.03 (\text{systolic BP}) - 0.04 (\text{eGFR}) + 2.75 (\text{WHR}) + 0.01 (\text{ALP}) -2.99) \text{ X } \log_2]}$$

Table 5: Clinical interpretation of effect of each factor on ACR (mg/mmol) and examples of possible real clinical cases

Additive contribution of each independent variable to estimated ACR expressed as a percentage increase				**Simulations (individual patients)**										
Additional percentage to estimated ACR relative to preceding simulated client	95% CI			*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*
Aboriginal ethnicity	47	9	98	TSI	Aboriginal	Aboriginal	Aboriginal	Aboriginal	Aboriginal	Aboriginal	Aboriginal	Aboriginal	Aboriginal	Aboriginal
Female sex	15	-14	54	Male	Male	Female	Female	Female	Female	Female	Female	Female	Female	Female
Age (-10 years)	16	4	27	45	45	45	55	55	55	55	55	55	55	55
Microscopic-haem	146	76	243	Absent	Absent	Absent	Absent	Present	Present	Present	Present	Present	Present	Present
Diabetes	186	108	293	Absent	Absent	Absent	Absent	Absent	Present	Present	Present	Present	Present	Present
ACEI/ARB	136	70	227	Absent	Absent	Absent	Absent	Absent	Absent	Present	Present	Present	Present	Present
Systolic BP (+10 mmHg)	24	16	31	125	125	125	125	125	125	125	135	135	135	135
eGFR (-10 ml/min/1.73m^2)	26	20	31	90	90	90	90	90	90	90	90	80	80	80
WHR (+ 0.1 units)	21	1	43	0.90	0.90	0.90	0.90	0.90	0.90	0.90	0.90	0.90	1.00	1.00
ALP (+ 10 U/L)	6	2	10	115	115	115	115	115	115	115	115	115	115	125
Estimated ACR (mg/mmol)				**1.3**	**1.9**	**2.18**	**1.87**	**4.58**	**13.12**	**30.96**	**39.09**	**50.64**	**61.03**	**64.87**

Interpretation: In this population, compared to client 1, client 2 has 147% higher estimated ACR (1.9 v 1.3 mg/mmol), thus Aboriginal ethnicity has a 47% additive contribution to ACR than the TSI client indicated by client 1. Compared to client 2, client 3 has 115% higher estimated ACR (2.2 v 1.9 mg/mmol), thus females sex has a 15% additive contribution to ACR in clients without diabetes in this population.