Check for updates

Canadian Society of Nephrology/ Société canadienne de néphrologie CSN/SCN

CANADIAN JOURNAL OF KIDNEY HEALTH AND DISEASE
Journal canadien de la santé et de la maladie rénale

Original Clinical Research Quantitative

Canadian Journal of Kidney Health and Disease
Volume 12: 1–11
© The Author(s) 2025
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/20543581251363126
journals.sagepub.com/home/cjk

Sage

Cardiometabolic Biomarkers and Prediction of Kidney Disease Progression: The eGFR Cohort Study

Elizabeth L. M. Barr[1,2], Federica Barzi[1,3], Phillip Mills (Kulkalgal)[4], Maria Nickels[1], Sian Graham[1], Odette Pearson[5], Varuni Obeyesekere[6], Wendy E. Hoy[7], Graham R. D. Jones[8,9], Paul D. Lawton[1,10], Alex D. H. Brown[11,12], Mark Thomas[13], Ashim Sinha[14], Alan Cass[1], Richard J. MacIsaac[6,15,16], Louise J. Maple-Brown[1,17,*] and Jaquelyne T. Hughes (Wagadagam)[1,17,18,*]

Abstract

Background: Traditional markers modestly predict chronic kidney disease progression in Aboriginal and Torres Strait Islander people. Therefore, we assessed associations of cardiometabolic and inflammatory clinical biomarkers with kidney disease progression among Aboriginal and Torres Strait Islander people with and without diabetes.

Objectives: To identify cardiometabolic and inflammatory clinical biomarkers that predict kidney disease progression in Aboriginal and Torres Strait Islander people.

Design: Prospective observational cohort study

Setting: Northern Territory, Australia

Participants: Aboriginal and Torres Strait Islander participants of the estimated glomerular filtration rate (eGFR) study with (n = 218) and without diabetes (n = 278)

Measurements: Baseline biomarkers (expressed as 1 standard deviation increase in logarithmic scale), plasma kidney injury molecule-1 (pKIM-1) (pg/ml), high-sensitivity troponin-T (hs-TnT) (ng/L), troponin-I (hs-TnI) (ng/L), and soluble tumor necrosis factor receptor-1 (sTNFR-1) (pg/ml) were assessed in 496 adults. Annual change in eGFR (ml/min/1.73 m^2) and a composite kidney outcome (first of ≥30% eGFR decline with follow-up eGFR <60 ml/min/1.73 m^2, initiation of kidney replacement therapy or kidney disease-related death) over a median of 3 years.

Methods: Linear regression estimated annual change in eGFR (ml/min/1.73 m^2). Cox proportional hazards regression estimated hazard ratio (HR) and 95% CI for developing a combined kidney health outcome.

Results: In individuals with diabetes, but not those without diabetes, higher baseline hs-TnT (−2.1 [−4.1 to −0.2], $P = .033$) and sTNFR-1 (−1.8 [−3.5 to −0.1], $P = .039$) predicted mean (95% CI) eGFR change, after adjusting for age, gender, baseline eGFR, and urinary albumin-to-creatinine ratio. Baseline variables explained 11% of eGFR decline variance; increasing to 27% ($P < .001$) with biomarkers. In diabetes, hs-TnT and hs-TnI were significantly associated with increased risk of kidney health outcomes.

Limitations: Limitations included potential chronic kidney disease misclassification from single creatinine and albumin measurements, limited adjustment for covariates due to a small sample size, and short follow-up restricting long-term outcome assessment.

Conclusions: Cardiovascular, kidney, and inflammatory biomarkers are likely associated with kidney function loss in diabetes, with particularly prominent associations for cardiac injury markers.

Abrégé

Contexte: Les marqueurs traditionnels sont des prédicteurs modérés de la progression de l'insuffisance rénale chronique (IRC) chez les Aborigènes et les Insulaires du Détroit de Torres. Nous avons évalué les associations de biomarqueurs cliniques cardiométaboliques et inflammatoires avec la progression de l'IRC dans ces populations, auprès d'individus atteints ou non de diabète.

Objectif: Identifier les biomarqueurs cliniques cardiométaboliques et inflammatoires qui prédisent la progression de l'insuffisance rénale chez les Aborigènes et les Insulaires du Détroit de Torres.

Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 License (https://creativecommons.org/licenses/by-nc/4.0/) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access pages (https://us.sagepub.com/en-us/nam/open-access-at-sage).

Conception: Étude de cohorte observationnelle prospective
Cadre: Territoire du Nord, Australie
Sujets: Les Aborigènes et Insulaires du Détroit de Torres, diabétiques (n=218) ou non (n=278), participant à l'étude « eGFR cohort study ».
Mesures: Les biomarqueurs initiaux (exprimés par une augmentation de l'écart-type de 1 échelle logarithmique), la protéine KIM-1 plasmatique (pKIM-1 — plasma Kidney Injury Molecule-1) en pg/ml, la troponine-T de haute sensibilité (hs-TnT) en ng/l, la troponine-I (hs-TnI) en ng/l et le récepteur-1 soluble du facteur de nécrose tumorale (sTNFR-1) en pg/ml ont été évalués chez 496 adultes. On a également examiné la variation annuelle du débit de filtration glomérulaire estimé (DFGe) (ml/min/1,73 m^2) et d'un résultat clinique composite de santé rénale (premier déclin du DFGe $\geq$30 % avec DFGe de suivi $<$ 60 ml/min/1,73 m^2, amorce d'un traitement de substitution rénale ou décès lié à une néphropathie) sur une durée médiane de 3 ans.
Méthodologie: La variation annuelle du DFGe (ml/min/1,73 m^2) a été estimée par régression linéaire. Le rapport de risque (RR) a été estimé par régression des risques proportionnels de Cox avec IC à 95 % pour le développement d'un résultat clinique composite de santé rénale.
Résultats: Chez les sujets diabétiques, des valeurs initiales plus élevées du hs-TnT (-2,1 [-4,1 à -0,2], p=0,033) et du sTNFR-1 (-1,8 [-3,5 à -0,1], p=0,039) ont prédit une variation moyenne (IC à 95 %) du DFGe, après correction selon l'âge, le sexe, le DFGe initial et le rapport albumine/créatinine urinaire, ce qui n'était pas le cas de sujets non-diabétiques. Les variables initiales pouvaient expliquer 11 % de la variation du déclin du DFGe; cette proportion augmentait à 27 % ($p<0,001$) avec les biomarqueurs. Chez les diabétiques, le hs-TnT et le hs-TnI ont été significativement associés à un risque accru d'issues de santé rénale.
Limites: La possible erreur de classification de l'IRC à partir de mesures uniques de créatinine et d'albumine, la correction limitée des covariables en raison de la petite taille de l'échantillon et la courte durée du suivi qui a empêché l'évaluation des résultats cliniques à long terme.
Conclusion: Les biomarqueurs cardiovasculaires, rénaux et inflammatoires sont probablement associés au déclin de la fonction rénale chez les diabétiques, et cette association serait particulièrement importante pour les marqueurs de lésions cardiaques.

Keywords
inflammatory markers, novel biomarkers, kidney disease progression, First Nations, epidemiology

Received: December 19, 2024; accepted: June 4, 2025.

[1]Menzies School of Health Research, Charles Darwin University, Casuarina, NT, Australia
[2]Baker Heart and Diabetes Institute, Melbourne, VIC, Australia
[3]UQ Poche Centre, The University of Queensland, Brisbane, Australia
[4]James Cook University, Cairns, QLD, Australia
[5]South Australian Health and Medical Research Institute, Adelaide, Australia
[6]Department of Endocrinology & Diabetes, St Vincent's Hospital Melbourne, Fitzroy, VIC, Australia
[7]The University of Queensland, Brisbane, Australia
[8]St Vincent's Hospital, SydPath, Sydney, NSW, Australia
[9]Department of Medicine, University of New South Wales, Sydney, Australia
[10]Monash University, Melbourne, VIC, Australia
[11]Indigenous Genomics, Telethon Kids Institute, Adelaide, SA, Australia
[12]National Centre for Indigenous Genomics, Australian National University, Adelaide, SA, Australia
[13]Royal Perth Hospital, Perth, WA, Australia
[14]Diabetes and Endocrinology, Cairns Base Hospital, Cairns, QLD, Australia
[15]Department of Medicine, University of Melbourne, Fitzroy, VIC, Australia
[16]Australian Centre for Accelerating Diabetes Innovations, University of Melbourne, Parkville, VIC, Australia
[17]Royal Darwin Hospital, Tiwi, NT, Australia
[18]Flinders Health and Medical Research Institute, College of Medicine and Public Health, Flinders University, Tiwi, NT, Australia

*Louise J. Maple-Brown and Jaquelyne T Hughes (Wagadagam) made equal contribution as senior authors.

Corresponding Author:
Elizabeth L. M. Barr, Menzies School of Health Research, Charles Darwin University, PO Box 41096, Casuarina, NT 0811, Australia.
Email: Elizabeth.barr@menzies.edu.au

General Audience Summary

The known. Aboriginal and Torres Strait Islander peoples urgently seek programs to slow chronic kidney disease progression. Clinical tests, like albuminuria and estimated kidney filtration rate, help detect chronic kidney disease, but additional markers could enable earlier interventions. **The new:** Heart, kidney, and inflammation markers, particularly heart damage markers, showed strong associations with worsening kidney function in diabetes. **The implications:** The findings support developing a clinical tool using routinely available biomarkers to improve early kidney disease detection and management tailored to meet the healthcare access priorities of Aboriginal and Torres Strait Islander peoples and reduce the burden of undiagnosed chronic kidney disease.

Introduction

Chronic kidney disease (CKD) affects 9% of the global population, but disproportionately impacts people experiencing socio-economic disadvantage,[1] and among First Nations populations.[2] In Australia, Aboriginal and Torres Strait Islander peoples are six times more likely to have kidney failure and four times more likely to die with CKD compared to non-First Nations Australians.[3] Despite this, Aboriginal and Torres Strait Islander peoples continue to draw on their strong and continuous cultures, and clinical and research expertise to improve kidney health and well-being.[4,5]

Albuminuria and estimated glomerular filtration rate (eGFR) are key measures for detecting and managing CKD,[6,7] especially in Aboriginal and Torres Strait Islander peoples, as albuminuria is a sensitive marker of CKD disease risk and progression that often emerges at an early age before diabetes and hypertension.[8,9] Identifying pre-clinical markers could enable earlier detection, as evidence suggests myocardial and kidney microvascular disease, driven by subclinical inflammation, contributes to heart and kidney dysfunction.[10-13] Few studies have assessed novel biomarkers concurrently in populations with and without diabetes[12,14] which is essential for assessing the role of inflammatory, cardiac and kidney biomarkers in predicting kidney disease progression across the glycemic spectrum.

Understanding the contributions of cardiometabolic and inflammatory biomarkers to predicting kidney disease progression in Aboriginal and Torres Strait Islander populations is essential given the high prevalence of diabetes, kidney disease and cardiovascular diseases, and background inflammation burden.[15] The eGFR Follow-up Study was a longitudinal cohort study that tracked kidney function over time in Aboriginal and Torres Strait Islander adults to identify patterns and predictors of CKD progression.[16] Aboriginal and Torres Strait Islander people seek improved kidney health and collaborated on the eGFR study, contributing health data from diverse regions of Australia.[16,17] This study aimed to firstly evaluate in Aboriginal and Torres Strait Islander peoples the associations of plasma levels of kidney injury molecule-1 (pKIM-1), high-sensitivity troponin-T (hs-TnT), and high-sensitivity troponin-I (hs-TnI) with kidney disease progression, after accounting for baseline albuminuria and eGFR levels. It also examined whether these associations were stronger among individuals with type 2 diabetes compared to those without. Building on our previous findings on serum tumor necrosis factor receptor-1 (sTNFR-1) levels predicting eGFR decline,[18] the study secondly assessed whether the prediction of kidney disease progression could be improved by jointly considering pKIM-1, hs-TnT, hs-TnI, and sTNFR-1 with baseline urinary albumin-to-creatinine ratio (uACR) and eGFR. It was hypothesized that these cardiometabolic and inflammatory markers would be important predictors of CKD progression, with stronger associations observed for those with type 2 diabetes.

Participants

Between 2007 and 2011, the eGFR study recruited 654 Aboriginal and Torres Strait Islander participants aged ≥16 years from health services or the community across 20 sites in four large regions, including remote locations where high rates of kidney disease were identified.[8,16] Convenience sampling was used to recruit participants from five pre-defined strata: (1) "healthy" people without diabetes, hypertension, CKD, or albuminuria; (2) participants with physician-diagnosed diabetes or albuminuria and eGFR (4 variable Modification in Diet of Renal Disease equation) >90 ml/min per 1.73 m^2; (3) eGFR 60–90 ml/min per 1.73 m^2; (4) eGFR 30–59 ml/min per 1.73 m^2; (5) eGFR 15–29 ml/min per 1.73 m^2. Individuals were ineligible if they had rapidly changing kidney function, were receiving dialysis or had a kidney transplant, were pregnant or breastfeeding, or had an allergy to iodine-based contrast media.

Participants provided written informed consent, and ethics approval from the Northern Territory Department of Health and Menzies School of Health Research Human Research Ethics Committee, including the Aboriginal sub-committee [07/54]; Central Australian Human Research Ethics Committee [2008/04/06 and 12/41]; Western Australian Aboriginal Health Information and Ethics Committee [228-12/08]; Royal Perth Measurements Hospital Ethics Committee [2009/026]; and Cairns and Hinterland Health Services District Human Research Ethics Committee [08/QCH/022-523].

Aboriginal and Torres Strait Islander Research Governance

The eGFR study was co-designed and supported by researchers and clinicians, including Aboriginal and Torres Strait Islander researchers, clinicians, and communities in the participating regions. Written approvals from Aboriginal and

Torres Strait Islander community leaders and organizations, ensured the study aligned with local priorities. Aboriginal and Torres Strait Islander eGFR study researchers (PM, MN, SG, ADHB, OP, and JTH) are members of their communities and kinship networks. They contributed to all aspects of the study, including study design, community partnering activities, data collection, interpretation, manuscript drafts, and dissemination of study findings. The eGFR3 study Aboriginal and Torres Strait Islander Community Governance Group co-chaired by SG (members listed in the acknowledgments) gave support to this analysis of the eGFR study. The Center of Research Excellence in Aboriginal Chronic Disease Knowledge Translation and Exchange (CREATE) quality appraisal tool[19] enabled authors to appraise the quality of research and methods undertaken with Indigenous peoples' health data (see Supplementary Table S1). This partnership will inform research translation to ensure health policy, planning and care models benefit Aboriginal and Torres Strait Islander people and their communities.

Materials and Methods

Blood samples were collected, transported on ice and stored at −80°C. Plasma pKIM-1 was measured on a human TIM-1/KIM-1/HAVCR Immunoassay (R&D Systems; Bio-Techne, Minnesota, MN, USA). Serum hs-TnT was measured on an electro-chemiluminescence immunoassay on a COBAS e601 analyzer (Roche Diagnostics, Mannheim, Germany) (limit of detection of 3.0 ng/L), and hs-TnI on a chemiluminescence immunoassay on an Abbott Architect i4000SR analyzer (Abbott Laboratories, North Chicago, IL, USA; limit of detection of 1.9 ng/L). The limit of detection for hs-TnT was ≤3.0 ng/L, and that for hs-TnI was <2.0 ng/L, and participants were assigned a value half the detectable limit (n = 337 for hs-TnT and n = 23 for hs-TnI). sTNFR-1 was measured using a Human sTNFR-1 EIA- BIO 94 kit obtained from EKF diagnostics (Dublin, Ireland).[18]

Baseline height, weight, waist and hip circumference, and seated blood pressure (mean of three measures; Welch Allyn Medical Products, Skaneateles Falls, NY, USA) were measured. Self-reported gender (male or female), cigarette smoking status (current, ex-smoker and never smoked), and medical records for information about diabetes diagnosis, prescription of 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase inhibitor medicines (statins), and antihypertensive medicines (primarily angiotensin-converting enzyme inhibitors and angiotensin II receptor antagonists)[16,20] were collected. Measured GFR (mGFR) was obtained using an iohexol plasma disappearance technique over 4 hours. Clinically-measured HbA_{1c}, urine creatinine and albumin (to determine urine albumin-to-creatinine ratio, uACR), high-sensitivity C-reactive protein (hs-CRP), high-density lipoprotein (HDL), and total cholesterol were collected from accredited local laboratories.[16,20]

Direct research assessments occurred 2-4 years after baseline. Medical and pathology information, including deaths and commencement of kidney replacement therapy, was collected for those unavailable.[8]

Serum creatinine was measured in follow-up research examinations for 67% using an IDMS-aligned enzymatic method (Roche Diagnostics, Australia) from thawed frozen sera (–80°C) by a single laboratory (Melbourne Pathology, Melbourne, Australia). For the remaining participants, clinically measured serum creatinine was collected from local laboratories using IDMS-aligned assays, with measurements equally comparable in predicting kidney decline.[21] The 2009 CKD-EPI eGFR (ml/min per 1.73 m^2 per year) creatinine-based formula without correction for African Americans was calculated.[17] Analyses were repeated using the 2021 CKD-EPI eGFR creatinine-based formula.[22]

Outcome measures included annual change in CKD-EPI eGFR (CKD-EPI eGFR follow-up minus CKD-EPI eGFR baseline/follow-up period) and a combined kidney health outcome, defined as the first of the following: an absolute 30% decline in eGFR with a follow-up eGFR <60 ml/min per 1.73 m^2, kidney replacement therapy initiation or kidney disease-related death. Deaths occurring when eGFR was <15 ml/min per 1.73 m^2 were classified as deaths resulting directly from kidney disease. Participants were censored at the first kidney health outcome, and follow-up time ranged between 0.5 and 5.2 years. For participants who died or who commenced kidney replacement therapy, the local creatinine value preceding the kidney health outcome was used to calculate annual change in CKD-EPI eGFR.

Statistical Analysis

Detailed analyses are outlined in the Supplementary file. Non-normal distributions for pKIM-1, hs-TnT, hs-TnI, HbA1c, hs-CRP, and uACR were observed and transformed by taking the natural logarithm. Biomarkers were also categorized: pKIM1 as quartiles, and hs-TnT and hs-TnI into tertiles above the limit of detection compared to values in the undetectable range to account for non-normal distribution (hs-TnT: undetectable range ≤3.0 ng/L; tertiles within the detectable range: >3.0 to ≤5.8; >5.8 to <11.5; and ≥11.5 ng/L; and hs-TnI: undetectable range <2 ng/L; tertiles within the detectable range: 2 to <4; 4 to <5; ≥5 ng/L). Participant characteristics were presented for the cohort and compared by baseline diabetes status, follow-up status, and categories of pKIM-1, hs-TnT and hs-TnI using one-way analysis of covariance, Kruskal-Wallis tests and χ^2. Biomarker correlations were assessed with Spearman's rho. Analyses were stratified by diabetes, where diabetes was defined as medical record physician diagnosis or HbA_{1c} ≥48 mmol/mol (≥6.5%). Scatter plots of annual eGFR decline according to baseline pKIM-1, hs-TnT and hs-TnI were examined for those with and without diabetes.

Associations of baseline pKIM-1, hs-TnT and hs-TnI with (1) annual eGFR decline (ml/min per 1.73 m^2) was assessed with linear regression, and (2) time to combined kidney health outcome with Cox proportional hazards regression. Non-linear associations were assessed and biomarkers were modeled as log-transformed variables (expressed as 1 standard deviation (SD)) and as categorical variables (with the first group as the reference). Models were adjusted for gender, age, CKD-EPI eGFR and uACR at baseline. Initially, each biomarker was modeled separately, and after using multiple imputation by chained equations (MICE) to impute missing values in each biomarker (pKIM-1 (n = 63), hs-TnT (n = 14), hs-TnI (n = 113), sTNFR-1 (n = 44)), all biomarkers were modeled together. Interactions between each biomarker and diabetes (diabetes or no diabetes) were assessed with the Wald test. The proportion of the variance in annual eGFR decline that was explained by the models with and without pKIM-1, hs-TnT, hs-TnI and sTNFR-1 was assessed with the adjusted-R^2 statistic. Harrell's c-statistic was calculated to assess whether adding biomarkers to a multivariate model with age, gender, baseline CKD-EPI eGFR and uACR improved model discrimination between participants who experienced and did not experience the combined kidney health outcome.

Sensitivity analyses included removing participants taking statins (n = 104) as previous studies have indicated that statins may have an anti-inflammatory effect,[23] excluded participants with a baseline CKD-EPI eGFR <30 ml/min/1.73 m^2 (n = 16), and those with macroalbuminuria (uACR ≥30 mg/mmol) (n = 73) to assess the potential impact of reverse causality between low eGFR or albuminuria and biomarker levels. Analyses were undertaken in Stata (version 17.0; College Station, TX, USA), and P values <.05 were considered statistically significant.

Results

Baseline Associations

Supplementary Figure S1 outlines data available for analysis. Of the 551 baseline Aboriginal and/or Torres Strait Islander participants with available data, 496 (90%) were followed-up. Exclusions included: follow-up data was <6 months (n = 5), lost to follow-up (n = 8), and missing follow-up enzymatic creatinine measures (n = 41). In addition, owing to sample availability, there were missing data for pKIM-1 (n = 63), hs-TnT (n = 14), hs-TnI (n = 113), and sTNFR1 (n = 44) analysis.

Of the 496 participants, 307 (62%) were female, 218 (44%) had diabetes, 212 (43%) had microalbuminuria or macroalbuminuria, and 68 (14%) had an eGFR of <60 ml/min per 1.73 m^2 at baseline (Table 1). Those with diabetes showed unfavorable biomarker levels and cardiometabolic profiles (Table 1). Participants excluded at follow-up (n = 55) were younger and had a favorable chronic conditions risk factor profile (Supplementary Table S2). Those with higher pKIM-1, hs-TnT, and hs-TnI had a worse cardiometabolic risk profile (Supplementary Tables S3-S5). While pKIM-1 and hs-TnT were moderately correlated with age, uACR, CKD-EPI eGFR, and HbA_{1c}, hs-TnI was not (Supplementary Tables S6 and S7). While higher pKIM-1 and hs-TnT levels were associated with higher uACR and lower CKD-EPI eGFR baseline levels, weaker associations were observed for hs-TnI (Supplementary Figures S2-S3).

Annual CKD-EPI eGFR Decline Over Follow-Up According to Biomarker Levels at Baseline

The median (25^{th}, 75^{th} percentile) annual CKD-EPI eGFR change was −2.4 (−0.5 to −5.5) ml/min/1.73 m^2 over a follow-up of 3.0 (2.5, 3.3) years. Figure 1 shows greater annual eGFR decline across increasing levels of baseline pKIM-1 (pg/ml) and hs-TnT (ng/L) particularly in those with diabetes. The decline was steeper for hs-TnT than for pKIM-1, and a less marked decline across increasing hs-TnI levels.

Associations of Biomarkers With Annual CKD-EPI eGFR Decline in Those With and Without Diabetes

Supplementary Tables S8-S10 show the coefficients (reflecting the slope of eGFR decline in ml/min/1.73 m^2 per year) for pKIM-1, hs-TnT, and hs-TnI. All biomarkers showed strong associations with annual eGFR decline in those with diabetes after adjusting for baseline age, gender and eGFR. Further adjustment for baseline uACR attenuated the associations but these remained statistically significant. Interaction with diabetes status was significant for pKIM-1 (P = .003), hs-TnT (P = .007), and hs-TnI (P = .005).

In those with diabetes, a model with age, gender, baseline eGFR CKD-EPI, and uACR explained 11% of the variance in eGFR decline. Adding pKIM-1 (13%, P = .02), hs-TnT (21%, P < .001), hs-TnI (14%, P < .02), or all biomarkers, including sTNFR-1 (27%, P < .001), improved the model. Figure 2 shows that hs-TnT and sTNFR-1 remained significantly associated with eGFR decline, while pKIM-1 and hs-TnI demonstrated borderline significance. Findings were similar after using the 2021 CKD-EPI eGFR (race free) equation, excluding participants taking HMG-CoA inhibitors, or those with a CKD-EPI eGFR <30 ml/min/1.73 m^2 (Supplementary Figure S6), and after further adjustment for hypertension, blood pressure, BMI, waist circumference, HbA1c, current smoking, or hs-CRP (Supplementary Figure S7). Associations for pKIM-1 and hs-TnT were attenuated in those without macroalbuminuria (Supplementary Figure S6).

Fifty-six participants progressed to the combined kidney health outcome. In models adjusted for age, gender, baseline eGFR, and uACR, hs-TnT and hs-TnI, but not pKIM-1, were significantly associated with the combined kidney health outcome in those with diabetes (Supplementary Table S11).

Table 1. Characteristics of the Study Population.

Study population characteristics	No diabetes	Diabetes	Total
N	278	218	496
Age, years	40 (±14)	52 (±12)	46 (±14)
Ethnicity			
Aboriginal	190 (68%)	160 (73%)	350 (71%)
Torres Strait Islander	57 (21%)	41 (19%)	98 (20%)
Aboriginal and Torres Strait Islander	31 (11%)	17 (8%)	48 (10%)
Female	170 (61%)	137 (63%)	307 (62%)
pKIM-1, pg/ml	41 (29, 61)	82 (54, 159)	55 (35, 95)
hs-TnT, ng/l	2 (2, 117.8) n = 277	2 (2, 213.2) n = 205	2 (2, 213.2) n = 482
hs-TnI, ng/l	3 (1, 56) n = 219	3 (1, 36) n = 164	3 (1, 56) n = 383
sTNFR-1, pg/ml	1509 (1242, 1886) n = 256	1822 (1430, 2512) n = 196	1622 (1284, 2146) n = 452
Currently smoking	137 (50%) n = 275	61 (29%) n = 213	198 (41%) n = 488
Previous myocardial infarction or ischaemic heart disease, n (%)	10 (4%) n = 270	36 (18%) n = 205	46 (10%) n = 475
hs C-reactive protein, mg/L	6.0 (3.0, 11.0) n = 271	5.9 (3.0, 12.0) n = 207	6.0 (3.0, 11.0) n = 478
BMI, kg/m^2	28.9 (±6.8) n = 276	32.6 (±7.2) n = 216	30.5 (±7.2) n = 492
Waist circumference, cm	97.1 (±15.9) n = 269	108.7 (±14.7) n = 204	102.1 (±16.4) n = 473
Waist to hip ratio	0.9 (±0.1) n = 269	1.0 (±0.1) n = 200	0.9 (±0.1) n = 469
Systolic blood pressure, mm Hg	115.5 (±16.0) n = 273	120.9 (±18.0) n = 217	117.9 (±17.1) n = 490
Diastolic blood pressure, mm Hg	74.0 (±10.1) n = 273	75.1 (±10.4) n = 217	74.5 (±10.3) n = 490
Anti-hypertensive medicine use, n (%)	51 (18%)	139 (64%)	190 (38%)
HbA1c, mmol/mol	39 (±4) n = 274	67 (±22) n = 212	51 (±20) n = 486
HbA1c, %	5.7 (±0.4) n = 274	8.2 (±2.0) n = 212	6.8 (±1.8) n = 486
Total cholesterol, mmol/L	5.1 (±1.0) n = 272	4.5 (±1.0) n = 210	4.8 (±1.1) n = 482
Statin use, n (%)	29 (10%)	104 (48%)	133 (27%)
HDL, mmol/L	1.1 (±0.4) n = 268	1.0 (±0.3) n = 204	1.1 (±0.3) n = 472
Total chol/HDL ratio	4.8 (±1.6) n = 268	4.7 (±1.5) n = 205	4.8 (±1.5) n = 473
Triglycerides, mmol/L	1.6 (1.2, 2.3) n = 272	2.1 (1.5, 2.8) n = 210	1.8 (1.3, 2.5) n = 482
Albumin to creatinine ratio, mg/mmol	1.1 (0.6, 3.3)	9.8 (1.7, 69.2)	2.0 (0.7, 17.1)
Albuminuria			
Normoalbuminuria <3 mg/mmol	207 (74%)	77 (35%)	284 (57%)
Microalbuminuria ≥3 to <30 mg/mmol	42 (15%)	66 (30%)	108 (22%)
Macroalbuminuria ≥30 mg/mmol	29 (10%)	75 (34%)	104 (21%)
Measured GFR, ml/min/1.73 m^2	104.8 (±24.7) n = 267	96.7 (±36.3) n = 204	101.3 (±30.5) n = 471
CKD-EPI eGFRcr, ml/min per 1.73 m^2	99.1 (±23.5)	85.1 (±29.7)	93.0 (±27.3)
KDIGO CKD-EPI eGFRcr groups			
<60 ml/min per 1.73 m2	22 (8%)	46 (21%)	68 (14%)
≥60 to <90 ml/min per 1.73 m2	54 (19%)	56 (26%)	110 (22%)
≥90 ml/min per 1.73 m2	202 (73%)	116 (53%)	318 (64%)

Note. Data are mean (±SD), median (25th, 75th percentile), or number (%), except for hs-TnT data are median (range). Data include participants with complete data on pKIM-1, hs-TnT, hs-TnI, and sTNFR-1. n Values provided when these differ from full group numbers. Measured GFR (mGFR) was obtained using an iohexol plasma disappearance technique over 4 hours. CKD-EPI eGFR: The 2009 Chronic Kidney Disease Epidemiology Collaboration glomerular filtration rate estimating equation. KDIGO CKD-EPI eGFRcr groups: Kidney Disease: Improving Global Outcomes 2009 CKD-EPI eGFR (creatinine equation) groups.

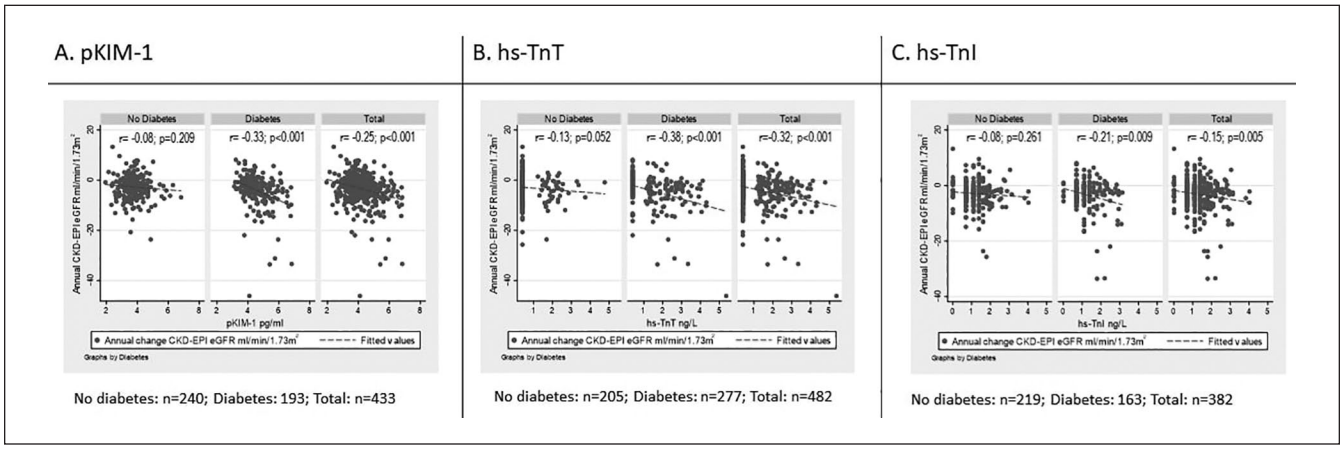
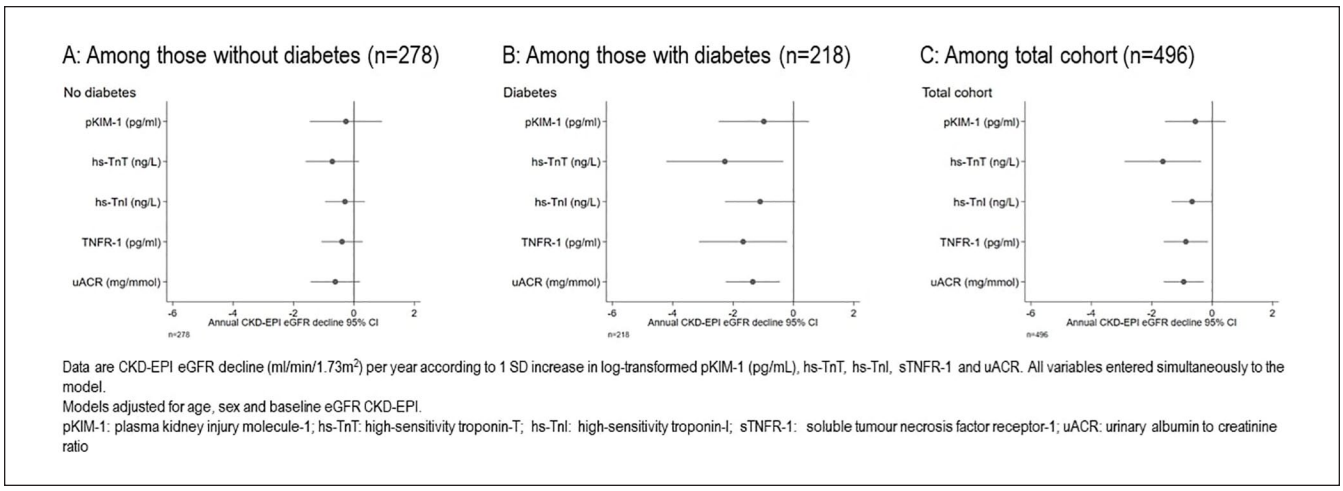


Figure 1. Annual CKD-EPI eGFR decline over a median of 3 years according to baseline levels of pKIM-1, hs-TnT and hs-TnI for participants with and without diabetes at baseline: the eGFR study.



Data are CKD-EPI eGFR decline (ml/min/1.73m^2) per year according to 1 SD increase in log-transformed pKIM-1 (pg/mL), hs-TnT, hs-TnI, sTNFR-1 and uACR. All variables entered simultaneously to the model.
Models adjusted for age, sex and baseline eGFR CKD-EPI.
pKIM-1: plasma kidney injury molecule-1; hs-TnT: high-sensitivity troponin-T; hs-TnI: high-sensitivity troponin-I; sTNFR-1: soluble tumour necrosis factor receptor-1; uACR: urinary albumin to creatinine ratio

Figure 2. Adjusted associations for pKIM-1, hs-TnT, hs-TnI, and sTNFR-1 with CKD-EPI eGFR decline: the eGFR study.

The c-statistic was 0.88 for the base model (age, gender, CKD-EPI eGFR and uACR) and this increased after adding hs-TnT (0.8907) or hs-TnI (0.8908). When all biomarkers were modeled together, associations for hs-TnT and hs-TnI remained of borderline significance (Figure 3), and the associations for pKIM-1 and sTNFR1 were attenuated. Among those without diabetes, none of the biomarkers showed a significant association with the combined kidney health outcome.

Discussion

This study of Aboriginal and Torres Strait Islander people, with and without diabetes, examined associations of novel circulating cardiovascular, kidney, and inflammation biomarkers with progression of CKD. Since study participants were recruited without acute-illness and within Australian regions known to have persistently high prevalence and incidence of dialysis-requiring CKD, this analysis provides valuable insights into the predictive role of these biomarkers in CKD progression over a median of 3 years. In individuals with diabetes, these biomarkers were significantly associated with kidney disease progression, with the troponins indicating cardiac injury showing stronger associations. We previously found that higher sTNFR1 concentrations were associated with kidney disease progression in individuals with, but not without diabetes.[18] Prediction of eGFR decline was significantly improved with the addition of these biomarkers to a model including uACR and eGFR; and associations remaining after adjusting for blood pressure, anthropometry, C-reactive protein or smoking. This underscores the need for broader assessments in kidney disease management of Aboriginal and Torres Strait Islander peoples.

A meta-analysis of plasma and urine biomarkers highlights their potential in predicting CKD. Plasma biomarkers,

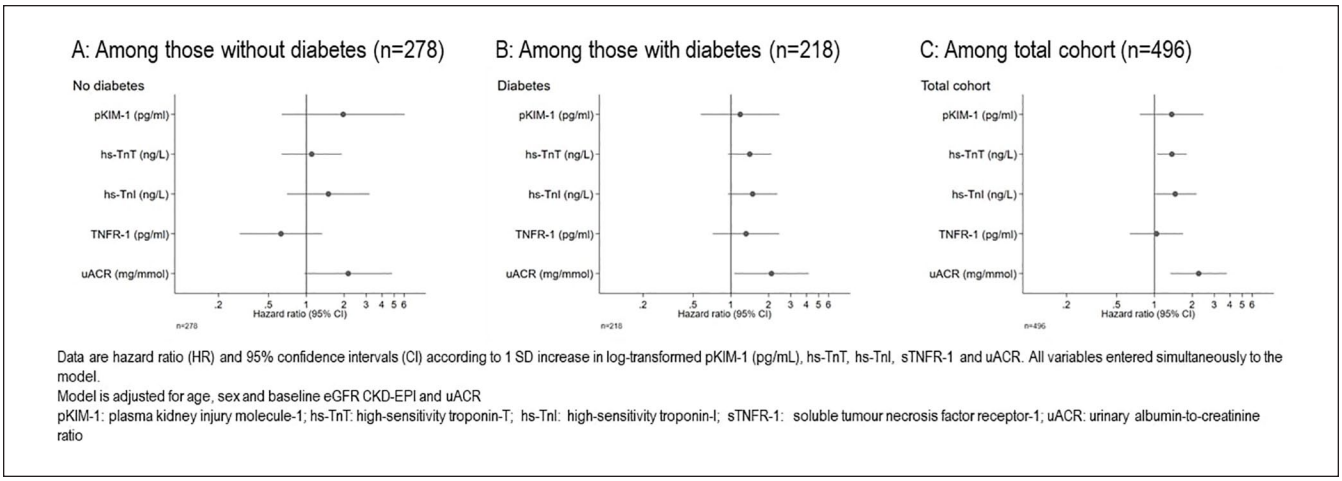


Figure 3. Risk of combined kidney health outcome for pKIM-1, hs-TnT, hs-TnI, and sTNFR-1 in those with and without diabetes: the eGFR study.

sTNFR1, sTNFR2, pKIM-1, and suPAR showed stronger associations with CKD outcomes than to urinary biomarkers.[11] Although some studies adjusted pKIM-1 data for uACR and eGFR, only two included studies, adjusted for additional markers (plasma TNFR1, plasma FGF23), showing significant associations for pKIM-1 with eGFR decline. We extend these findings, modeling pKIM-1, hs-TnT, hs-TnI, and sTNFR1 in those with and without diabetes. Among those with diabetes, higher pKIM-1 levels remained significantly associated with eGFR decline after adjusting for uACR and eGFR, but associations weakened when modeled with sTNFR1, hs-TnT, and hs-TnI. These findings highlight the potential of cardio-kidney-inflammatory biomarkers to identify rapid kidney disease progression in diabetes, and to improve care for Aboriginal and Torres Strait Islander peoples.

Elevated cardiac troponin commonly signify myocardial injury and aids myocardial infarction diagnosis.[24] High-sensitivity cardiac troponin, even within normal levels, is often raised in CKD.[25] While most studies show that high hs-TnT predicts CKD,[26,27] few report on hs-TnI.[28] In our study, we found that elevated hs-TnT levels (>3.0 ng/L) strongly predicted eGFR decline in those with diabetes, independent of other biomarkers like pKIM1 and sTNFR1. A similar association was observed for hs-TnI, though it added less predictive value. Differences in their predictive power may reflect hs-TnT's strong association with diabetes[29] and non-cardiovascular mortality.[30] We showed weak correlations for hs-TnI with uACR, CKD-EPI eGFR, and hs-TnT. Our study emphasizes that cardiovascular microvascular dysfunction could be a key driver of kidney disease progression, independent of other inflammatory mechanisms.

Biomarkers may become elevated as a result of kidney dysfunction, yet this might not be the primary mechanism responsible for high circulating levels.[31] Our analyses demonstrated moderate correlations between biomarkers and uACR or eGFR at baseline, with no evidence of statistical collinearity. We did not investigate causal mechanisms, but proving causality is less important for risk prediction. For clinical use, biomarkers must be easily measurable and affordable. Measurement of troponins with a readily available standardized assay could support kidney disease management.

Study participants were recruited from multiple Australian communities, including remote regions, enhancing the study's generalizability to other Aboriginal and Torres Strait Islander peoples and other ethnicities globally, especially First Nations populations disproportionately affected by diabetes and kidney disease and underrepresented in such research. It is among the few studies worldwide to evaluate novel biomarkers in a First Nations population.[32,33] Nonetheless, limitations exist. Remote locations meant multiple measurements of serum creatinine was challenging, and reliance on single creatinine and urinary albumin measurements could lead to misclassification. CKD clinical ascertainment requires two assessments 2 months apart. Biomarkers were assayed in thawed samples which might affect results, although prior reports indicate stability.[34,35] The sample size limited simultaneous adjustment of multiple clinical covariates, or exploration of metabolomics.[36] Residual confounding could have led to an overestimation of the results. While a median three-year follow-up period was useful for determining short time prediction, it restricted assessment of longer-term clinical outcomes, and associations in those without diabetes who experienced less kidney disease progression over the 3-year follow-up period. Ongoing follow-up within the eGFR study will provide over 10 years' hospital and mortality data, which will enable development and assessment of clinical CKD risk-prediction tools.

Most participants with diabetes in our study reported renin-angiotensin-aldosterone system inhibitor use, consistent with clinical recommendations at that time, preventing

sensitivity modeling. Sodium-glucose cotransporter-2 inhibitors (SGLT2i) and glucagon-like peptide-1 receptor agonists (GLP-1RA) were unavailable prior to 2015, when original data were collected, preventing assessment of their impact on our findings. These therapies reduce the risk of cardiovascular disease and slow chronic kidney disease progression.[37,38] Our study supports the potential role of hs-TnT, hs-TnI and sTNFR1 in CKD risk prediction, underscoring treatment targets. Indeed, research shows that GLP-1RA medicines improve inflammatory and oxidative markers,[39] and SGLT2i reduces pKIM1,[40] hs-TnT,[13] and sTNFR1[41] levels in type 2 diabetes.

The eGFR study is an Australian landmark kidney study that has been conducted in consultation with Aboriginal and Torres Strait Islander communities in its establishment and decade of continuity inclusive of negotiating study agreements informed by local community protocols, emergence of Indigenous research paradigms with Indigenous leadership and governance of the study growing beyond the research team to a dedicated Indigenous governance group. Importantly, this study highlights the potential role of cardiovascular, kidney and inflammatory biomarkers in predicting CKD progression, particularly in diabetes, within a population that experiences considerable and sustained health inequality and extraordinarily high burden of diabetes and CKD. The findings strongly support the development and evaluation of a CKD predictive algorithm that incorporates a wide range of clinical biomarkers suitable for routine clinical use, even in resource-limited settings. Future follow-up studies will be crucial to fully assess clinical outcomes related to eGFR decline.

Authors' Note

Prior publication in abstract form

Elizabeth L. M. Barr, Jaquelyne T Hughes, Federica Barzi, Varuni Obeyesekere, Wendy E Hoy, Kerin O'Dea, Graham RD Jones, Paul D. Lawton, Alex DH Brown, Mark Thomas, Ashim Sinha, Alan Cass, Maria Nickels, Richard J MacIsaac, Louise J Maple-Brown. Novel markers and prediction of kidney disease progression in Aboriginal and Torres Strait Islander people with and without diabetes: the eGFR study. The Australian Diabetes Congress Scientific Meeting, 2021, Online environment, Australia.

Acknowledgments

The authors gratefully acknowledge the data-owners, who are Aboriginal and Torres Strait Islander people who participated in the eGFR Study, and supported this analysis led by eGFR study researchers. The authors acknowledge the data sourced from the baseline study, the change in kidney function confirmed at the 3-year follow-up study, and considering the data meaning with support of Aboriginal and Torres Strait Islander researchers since baseline, and within the third phase of the study—eGFR3 Study Aboriginal and Torres Strait Islander Community Governance Group. Authors acknowledge and thank eGFR study staff, partner organizations, and eGFR3 study Aboriginal and Torres Strait Islander Community Governance Group (Helen Fejo-Frith (co-Chair), Natalie Hunter, Phillip Mills, Annette Stokes, Sian Graham (co-Chair)). The authors thank Dr. Kevin Warr and Dr. William Majoni for facilitating participant recruitment and follow-up at the sites of their employing organization and Loyla Leysley, Sian Graham, Mary Keta Ward, and Joseph Fitz for assistance with follow-up in their communities. The authors also thank Melbourne Pathology for providing the technical support in the enzymatic creatinine analysis, Roche Diagnostics for supplying the enzymatic creatinine reagent kit for the baseline study, and EKD diagnostics for their assistance in helping to source the sTNFR1 assay kits.

Ethical Considerations

Participants provided written informed consent and obtained ethics approval from the Northern Territory Department of Health and Menzies School of Health Research Human Research Ethics Committee, including the Aboriginal sub-committee [07/54]; Central Australian Human Research Ethics Committee [2008/04/06 and 12/41]; Western Australian Aboriginal Health Information and Ethics Committee [228-12/08]; Royal Perth Measurements Hospital Ethics Committee [2009/026]; and Cairns and Hinterland Health Services District Human Research Ethics Committee [08/QCH/022-523].

Consent to Participate

Participants provided written informed consent.

Consent for Publication

No individual person is identified in this manuscript.

Author Contributions

All authors have contributed significantly to this manuscript, agree with the content, and are collectively accountable for all aspects of the work. Specifically, ELM Barr conceived and designed the analysis, drafted the manuscript, analyzed and interpreted the data; F Barzi advised on the statistical analysis, interpreted the data, and revised the manuscript; P Mills, M Nickels, S Graham, WE Hoy, GRD Jones, PD Lawton, ADH Brown, M Thomas, A Sinha, and A Cass interpreted the data and revised the manuscript; O Pearson joined the third follow-up phase of the eGFR study and focused on Indigenous governance of the study including data sovereignty and thus contributed to informing the tri-governance arrangements and their terms of reference, advocated for the publication of this data to ensure that the community had the opportunity to benefit from research undertaken during the eGFR3 study, and reviewed the manuscript. V Obeyesekere undertook biomarker assays, interpreted the data, and revised the manuscript. RJ MacIsaac conceived the analysis, interpreted the data, and revised the manuscript. JT Hughes led community engagement and participant recruitment in several regions, collected and interpreted the data and revised the manuscript, led the eGFR Study since 2018, and leads the eGFR3 Study; LJ Maple-Brown conceived the eGFR study, led all aspects of the conduct of the study including data collection, interpreted the data, and revised the manuscript. All authors approved the final version.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: The eGFR Study was funded by the National Health and Medical

Research Council of Australia (NHMRC, Project Grants #545202, #1021460, and #GNT1184083), with additional support from SVHA Inclusive Health Innovation Fund, Kidney Health Australia, NHMRC Program Grant (#631947), the Colonial Foundation, Diabetes Australia Research Trust (Y19G-BARE), Rebecca L Cooper Foundation and SeaSwift, Thursday Island; ELMB was supported by a Diabetes Australia Research Trust Grant (Y19G-BARE), LJM-B was supported by NHMRC Fellowship/Investigator Grants (#605837, #1078477, and #1194698); OP is funded by an NHMRC Emerging Leader 2 grant (#GNT2026852); FB was supported by NHMRC Program Grant (#631947); JTH was supported by NHMRC Fellowship #1092576 and an RACP Jacquot Research Establishment Award, and NHMRC Emerging Leadership Fellowship (#1174758); PDL was supported by NHMRC Scholarship #1038721, an RACP Jacquot Research Establishment Award and an NHMRC early career fellowship (#1120640); WH directs the NHMRC-funded Center for Research Excellence in Chronic Kidney Disease (#1079502). ADHB was supported by a Viertel Senior Medical Research Fellowship and an NHMRC Senior Research Fellowship (#44126324). AC was supported by the National Health and Medical Research Council Investigator Grant (#1194677). RM was supported by an Australian Diabetes Society-Servier Diabetes Research Grant, an Australian Diabetes Society-AstraZeneca Diabetes Research Grant and St Vincent's Hospital Melbourne Research Endowment grants. The views expressed in this publication are those of the authors and do not reflect the views of the NHMRC. Funding bodies had no role in the study design, in the collection, analysis, or interpretation of data, in the writing of the manuscript, or in the decision to submit the manuscript for publication.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: MT, in the last 5 years, has received lecture fees and advisory board payments for cardiometabolic topics from AstraZeneca, Bayer, Boehringer Ingelheim, and Eli Lilly. RM reports no direct conflicts of interest to the work reported in this paper. However, RM has received research grants from Novo Nordisk, Servier, Medtronic, The Rebecca Cooper Medical Research Foundation, St Vincent's Research Foundation, The Juvenile Diabetes Research Foundation, Gray Innovations, The Diabetes Australia Research Trust/Program, and The National Health and Medical Research Council of Australia. RM also received honoraria for lectures from Eli Lilly, Novo Nordisk, Sanofi Aventis, AstraZeneca, Merck Sharp & Dohme, Norvartis, and Boehringer Ingelheim and has been or is on the advisory boards for Novo Nordisk, Boehringer Ingelheim-Eli Lilly Diabetes Alliance, AstraZeneca and Merck Shape and Dohme. Travel support for RM has been supplied by Novo Nordisk, Sanofi, Boehringer Ingelheim, and AstraZeneca. RM has been a principal investigator for industry-sponsored clinical trials run by Novo Nordisk, Sanofi, Bayer, Johnson-Cilag and Abbive. All other authors declare no conflict of interest to disclose.

Data Availability

The data pertaining to The eGFR cohort are stored at Menzies School of Health Research, Darwin, Northern Territory, Australia, and requests can be directed to the principal study investigator, Prof Jaqui Hughes (jaqui.hughes@flinders.edu.au) and Menzies eGFR chief study investigators Prof Louise Maple-Brown (louise.maple-brown@menzies.edu.au) and Elizabeth Barr (elizabeth.barr@menzies.edu.au), and subject to the terms and conditions outlined in the Menzies School of Health Research Data Sharing Agreement Guidelines. Requests can be considered within the eGFR3 Study tri-governance structure, comprising the Research Governance Group, the Aboriginal and Torres Strait Islander Community Governance Group and the Clinical Governance Group, and the relevant Ethics Committees including the Aboriginal and Torres Strait Islander sub-committee of the Human Research Ethics Committee of NT Health and Menzies School of Health Research.

ORCID iDs

Elizabeth L. M. Barr https://orcid.org/0000-0003-4284-1716
Graham R. D. Jones https://orcid.org/0000-0001-9109-7255
Alex D. H. Brown https://orcid.org/0000-0003-2112-3918
Richard J. MacIsaac https://orcid.org/0000-0001-8058-6977

Supplemental Material

Supplemental material for this article is available online.

References

1. Xie Y, Bowe B, Mokdad AH, et al. Analysis of the Global Burden of Disease study highlights the global, regional, and national trends of chronic kidney disease epidemiology from 1990 to 2016. *Kidney Int*. 2018;94(3):567-581.
2. Huria T, Pitama SG, Beckert L, et al. Reported sources of health inequities in Indigenous Peoples with chronic kidney disease: a systematic review of quantitative studies. *BMC Public Health*. 2021;21(1):1447.
3. Australian Institute of Health and Welfare. Chronic kidney disease in Aboriginal and Torres Strait Islander people 2011. Cat. no. PHE 151. Canberra: AIHW; 2011.
4. Western Desert Nganampa Walytja, Palyantjaku Tjutaku Aboriginal Corporation. Purple House. https://www.purplehouse.org.au/our-story. Accessed October 11, 2023.
5. Mick-Ramsamy L, Kelly J, Duff D, et al. *Catching Some Air—Asserting Aboriginal and Torres Strait Islander Information Rights in Renal Disease Project—The Final Report*. Darwin: Menzies School of Health Research; 2019.
6. Kidney Disease Improving Global Outcomes (KDIGO), CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int*. 2013;84(3):622-623.
7. Gansevoort RT, Matsushita K, van der Velde M, et al. Lower estimated GFR and higher albuminuria are associated with adverse kidney outcomes. A collaborative meta-analysis of general and high-risk population cohorts. *Kidney Int*. 2011;80(1):93-104.
8. Maple-Brown LJ, Hughes JT, Ritte R, et al. Progression of kidney disease in Indigenous Australians: the eGFR follow-up study. *Clin J Am Soc Nephrol*. 2016;11(6):993-1004.
9. Hoy WE, Wang Z, VanBuynder P, Baker PR, McDonald SM, Mathews JD. The natural history of renal disease in Australian Aborigines. Part 2. Albuminuria predicts natural death and renal failure. *Kidney Int*. 2001;60(1):249-256.

10. Zhou LT, Lv LL, Pan MM, et al. Are urinary tubular injury markers useful in chronic kidney disease? A systematic review and meta analysis. *PLoS ONE*. 2016;11(12):e0167334.
11. Liu C, Debnath N, Mosoyan G, et al. Systematic review and meta-analysis of plasma and urine biomarkers for CKD outcomes. *J Am Soc Nephrol*. 2022;33(9):1657-1672.
12. Anderson AH, Xie D, Wang X, et al. Novel risk factors for progression of diabetic and nondiabetic CKD: findings from the Chronic Renal Insufficiency Cohort (CRIC) study. *Am J Kidney Dis*. 2021;77(1):56-73.
13. Januzzi JL, Mohebi R, Liu Y, et al. Cardiorenal biomarkers, canagliflozin, and outcomes in diabetic kidney disease: the CREDENCE trial. *Circulation*. 2023;148(8):651-660.
14. Schrauben SJ, Shou H, Zhang X, et al. Association of multiple plasma biomarker concentrations with progression of prevalent diabetic kidney disease: findings from the Chronic Renal Insufficiency Cohort (CRIC) Study. *J Am Soc Nephrol*. 2021;32(1):115-126.
15. Australian Institute of Health and Welfare. Cardiovascular disease, diabetes and chronic kidney disease—Australian facts: aboriginal and Torres Strait Islander people. Cardiovascular, diabetes and chronic kidney disease series no. 5. Cat. no. CKD 5. Canberra: AIHW; 2015.
16. Maple-Brown LJ, Lawton PD, Hughes JT, et al. Study protocol—accurate assessment of kidney function in Indigenous Australians: aims and methods of the eGFR study. *BMC Public Health*. 2010;10:80.
17. Maple-Brown LJ, Hughes JT, Lawton PD, et al. Accurate assessment of kidney function in indigenous Australians: the estimated GFR study. *Am J Kidney Dis*. 2012;60(4):680-682.
18. Barr ELM, Barzi F, Hughes JT, et al. High baseline levels of tumor necrosis factor receptor 1 are associated with progression of kidney disease in indigenous Australians with diabetes: the eGFR follow-up study. *Diabetes Care*. 2018;41(4):739-747.
19. Harfield S, Pearson O, Morey K, et al. Assessing the quality of health research from an Indigenous perspective: the Aboriginal and Torres Strait Islander quality appraisal tool. *BMC Med Res Methodol*. 2020;20(1):79.
20. Hughes JT, Maple-Brown L, Thomas M, et al. Cross-sectional associations of albuminuria among Aboriginal and Torres Strait Islander adults: the eGFR study. *Nephrology*. 2016;23(1):37-45.
21. Barzi F, Jones GRD, Hughes JT, et al. Trajectories of eGFR decline over a four year period in an Indigenous Australian population at high risk of CKD-the eGFR follow up study. *Clin Biochem*. 2018;53:58-64.
22. Inker LA, Eneanya ND, Coresh J, et al. New creatinine- and cystatin C-based equations to estimate GFR without race. *N Engl J Med*. 2021;385(19):1737-1749.
23. Tonelli M, Sacks F, Pfeffer M, Jhangri GS, Curhan G; Cholesterol and Recurrent Events (CARE) Trial Investigators. Biomarkers of inflammation and progression of chronic kidney disease. *Kidney Int*. 2005;68(1):237-245.
24. Thygesen K, Alpert JS, Jaffe AS, et al. Fourth Universal Definition of Myocardial Infarction (2018). *J Am Coll Cardiol*. 2018;72(18):2231-2264.
25. Tang O, Daya N, Matsushita K, et al. Performance of high-sensitivity cardiac troponin assays to reflect comorbidity burden and improve mortality risk stratification in older adults with diabetes. *Diabetes Care*. 2020;43(6):1200-1208.
26. Welsh P, Woodward M, Hillis GS, et al. Do cardiac biomarkers NT-proBNP and hsTnT predict microvascular events in patients with type 2 diabetes? Results from the ADVANCE trial. *Diabetes Care*. 2014;37(8):2202-2210.
27. Kim Y, Matsushita K, Sang Y, et al. Association of high-sensitivity cardiac troponin T and natriuretic peptide with incident ESRD: the Atherosclerosis Risk in Communities (ARIC) Study. *Am J Kidney Dis*. 2015;65(4):550-558.
28. Ho JE, Hwang SJ, Wollert KC, et al. Biomarkers of cardiovascular stress and incident chronic kidney disease. *Clin Chem*. 2013;59(11):1613-1620.
29. Welsh P, Preiss D, Shah ASV, et al. Comparison between high-sensitivity cardiac troponin T and cardiac troponin I in a large general population cohort. *Clin Chem*. 2018;64(11):1607-1616.
30. Welsh P, Preiss D, Hayward C, et al. Cardiac troponin T and troponin I in the general population. *Circulation*. 2019;139(24):2754-2764.
31. Savoj J, Becerra B, Kim JK, et al. Utility of cardiac biomarkers in the setting of kidney disease. *Nephron*. 2019;141(4):227-235.
32. Pavkov ME, Nelson RG, Knowler WC, Cheng Y, Krolewski AS, Niewczas MA. Elevation of circulating TNF receptors 1 and 2 increases the risk of end-stage renal disease in American Indians with type 2 diabetes. *Kidney Int*. 2015;87(4):812-819.
33. Niewczas MA, Pavkov ME, Skupien J, et al. A signature of circulating inflammatory proteins and development of end-stage renal disease in diabetes. *Nat Med*. 2019;25(5):805-813.
34. Agarwal SK, Avery CL, Ballantyne CM, et al. Sources of variability in measurements of cardiac troponin T in a community-based sample: the atherosclerosis risk in communities study. *Clin Chem*. 2011;57(6):891-897.
35. Buchanan JL, Tormes Vaquerano J, Taylor EB. Isolated effects of plasma freezing versus thawing on metabolite stability. *Metabolites*. 2022;12(11):1098.
36. Moritz L, Schumann A, Pohl M, Köttgen A, Hannibal L, Spiekerkoetter U. A systematic review of metabolomic findings in adult and pediatric renal disease. *Clin Biochem*. 2024;123:110703.
37. de Boer IH, Khunti K, Sadusky T, et al. Diabetes management in chronic kidney disease: a consensus report by the American Diabetes Association (ADA) and Kidney Disease: Improving Global Outcomes (KDIGO). *Diabetes Care*. 2022;45(12):3075-3090.
38. Peng ZY, Yang CT, Lin WH, Yao WY, Ou HT, Kuo S. Chronic kidney outcomes associated with GLP-1 receptor agonists versus long-acting insulins among type 2 diabetes patients requiring intensive glycemic control: a nationwide cohort study. *Cardiovasc Diabetol*. 2023;22(1):272.
39. Bray JJH, Foster-Davies H, Salem A, et al. Glucagon-like peptide-1 receptor agonists improve biomarkers of inflammation and oxidative stress: a systematic review and meta-analysis of randomised controlled trials. *Diabetes Obes Metab*. 2021;23(8):1806-1822.
40. Sen T, Li J, Neuen BL, et al. Effects of the SGLT2 inhibitor canagliflozin on plasma biomarkers TNFR-1, TNFR-2 and KIM-1 in the CANVAS trial. *Diabetologia*. 2021;64(10):2147-2158.
41. Heerspink HJL, Perco P, Mulder S, et al. Canagliflozin reduces inflammation and fibrosis biomarkers: a potential mechanism of action for beneficial effects of SGLT2 inhibitors in diabetic kidney disease. *Diabetologia*. 2019;62(7):1154-1166.