

# Birthweight and the Prevalence, Progression, and Incidence of CKD in a Multideterminant Model in a High-Risk Australian Aboriginal Community



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**Introduction:** We have previously showed that albuminuria was associated with low birthweight in young adults in a remote Australian Aboriginal community that has high rates of kidney disease. Here we describe the association of birthweight with incidence and progression of kidney disease over time.

**Methods:** Among 695 members of an Aboriginal community with recorded birthweights, urine albumin creatinine ratio (ACR) and estimated glomerular filtration rate (eGFR) were measured at ages 5 to 40 years, and follow-up values were measured or imputed again a median of 11.6 years later. Prevalence of markers on each occasion and change over time were evaluated in the context of birthweights and other potentially significant factors.

**Results:** On the second screen, ACR was inversely and significantly correlated with birthweight and eGFR was directly correlated with birthweight. Increases in ACR and in proportions of persons who developed new-onset (incident) albuminuria between screens were higher in those of lower birthweights (<2.5 kg). Proportions of persons who lost  $\geq 20\%$  of their baseline eGFR were higher in the lower birthweight groups. Lower birthweights also amplified elevations of ACR associated with other risk factors, specifically higher body mass indexes (BMIs) and a prior history of poststreptococcal glomerulonephritis (PSGN). At both screens, progressively higher levels of ACR beyond the mid-microalbuminuria range were correlated with lower levels of eGFR.

**Conclusions:** Lower birthweight contributes to an excess of kidney disease and its progression in this population. Because an excess of low birthweight and episodes of PSGN are eminently preventable, substantial containment of kidney disease is feasible.

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**KEYWORDS:** albuminuria; Australian Aboriginal; birthweight; estimated glomerular filtration rate; kidney disease incidence and progression

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Since the 1980s, rates of kidney disease, hypertension, and diabetes have been high in Aboriginal Australians living in remote areas, and rates of kidney failure have been among the highest in the world.<sup>1,2</sup>

In one high-risk community, we showed that the underlying kidney disease is marked by albuminuria.<sup>3–5</sup> We described its community-wide distribution and associations, the discernible risk factors, its association with loss of excretory renal function,<sup>1–5</sup> and the

response to treatment with angiotensin-converting enzyme inhibition.<sup>4,6</sup> We have also emphasized that albuminuria predicts, not only all renal deaths, but most nonrenal natural deaths as well.<sup>7,8</sup>

In that first community-wide study, factors that were significantly and independently correlated with albuminuria in young adults included older age, female gender, higher BMI, a history of PSGN, higher blood glucose levels, and lower birthweights.<sup>3,9–12</sup> That was the first description of the association of birthweight with albuminuria on a community basis. We now confirm such a relationship on repeat testing, approximately 10 years later, and show that lower birthweights predispose to progression of albuminuria and development of “incident” albuminuria over time. Furthermore, we show that the effects of lower

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birthweights on albuminuria are amplified in the presence of other risk factors.

## METHODS

Birthweights were first recorded in this community in 1956; they have been documented in community and hospital-birth registers, and, more recently, individual health records.

From July 1992 to the end of 1998, and again in 2004 to 2006, health screens were offered to all ambulatory volunteers age 5+ years in this Aboriginal community; more than 80% of the age-eligible population participated each time. Although everyone is always welcome to participate, this analysis does not include persons who were on dialysis or had a kidney transplant at the first screen.

Testing in those screens has included height, weight, waist, blood pressure, skin examination, urinary ACR (mg/mmol), and for those age 10+ years, levels of serum creatinine, as well as lipids, liver function tests, C-reactive protein (mg/l), and assessment of glycemia. At the first screen, diabetes was defined by a diagnosis in the medical record, or by World Health Organization levels of glycemia. Examinations at follow-up also included HbA1c levels in all subjects. Urine albumin was measured by radioimmunoassay, and eGFR (ml/min per 1.73 m<sup>2</sup>) was estimated from the modification of diet in renal disease formula for adults.<sup>13</sup> Results by the Chronic Kidney Disease-Epidemiology Collaboration formula were similar and provided no additional insights. eGFR in those aged 10 to <18 years at screening was calculated by the Schwartz formula<sup>14</sup>; however, those values in the first screen in late teenagers were seriously discordant with simultaneous modification of diet in renal disease values. Thus, we do not present eGFR values in persons aged <18 years at screening, nor calculations of eGFR changes in those who progressed from childhood to adulthood between the screens.

This was a retrospective prospective study, based on all persons with recorded birthweights, who were age 5 to <41 years at the first screen, and had measurements of urine ACR and (for those aged ≥10 years) serum creatinine at that time, and for whom follow-up values of ACR and eGFR were available, either measured in the second screen or imputed, a median of 11.6 years later. For people who started dialysis before the second screen, ACR and eGFR values of 256 mg/mmol and 8 ml/min per 1.73 m<sup>2</sup>, respectively, were ascribed to them on the dates of starting dialysis if no other results were available.

Relationships between renal parameters and birthweight as a continuous or categorical variable, by sex

and screen, were evaluated using univariable and multivariable least-squares regression. Urinary ACR was analyzed as the log<sub>2</sub> function of the continuous ACR variable, which renders its distribution more normal. Relationships of continuous renal parameters over the 3 categories of birthweight, and, within them, by categories of BMI around the adult median values and by PSGN history, were assessed. They are demonstrated by box plots, with interquartile ranges, median, upper, and lower adjacent values as whiskers, and outliers, and the Cusick nonparametric test for trend applied.

Differences in physical and biochemical characteristics between first observations and follow-up were tested using paired *t*-tests if data were continuous, and 2-sample proportion tests if categorical. Relationships between eGFR and ACR were explored with linear regression and associated *P* values, and their quadratic predictions represented graphically. Changes in ACR over time (follow-up ACR minus ACR at the first screen) were evaluated as the untransformed value and, for values greater than 1, as the log<sub>2</sub> function of that change. Proportions of people with incident albuminuria at follow-up, at thresholds of 3.4 and 34 g/mol were calculated in persons with ACR levels below those thresholds at the first screen. Changes in eGFR over time were the difference between follow-up eGFRs and eGFR on the first screen.

Proportions of people with various degrees of loss of eGFR between screens were calculated as potential parameters of progression. All these renal markers were examined in relation to birthweight as a continuous variable and categories of birthweight. Models of the prevalence of albuminuria at baseline and on follow-up, and of definitions of incident albuminuria, were evaluated by logistic regression in relation to birthweight, adjusted for other significant factors, including adult median BMI and PSGN history. Trends across categories were evaluated by either nptrend or tabodds tests. Analyses were conducted using Stata SE 16.1 (Stata Corp, College Station, TX) with a significance level of 0.05.

## RESULTS

A total of 830 persons aged 5 to <41 years with recorded birthweights participated in the first screen. Of these, 695 participated in the second screen or had follow-up values of ACR and eGFR imputed if renal failure had developed in the interim: these 695 persons constitute our study cohort. Among the 135 on whom there were no follow-up values, 23 had died of unnatural causes (eg, suicide, homicide, accidents) and 17 had died of natural causes, from a variety of conditions

(but excluding renal failure). The remaining 95 were absent from the community, pregnant or breastfeeding, could not be reached or declined, or were not available to participate in the second screen. At the first screen, there were no significant differences between these 135 people with no follow-up values and the 695 people in the study cohort, as shown in [Supplementary Table S1](#). However, because all who developed end-stage kidney failure over follow-up had been relegated to the study cohort with imputed values of ACR and eGFR when they started dialysis, none were allocated to the 135 people excluded from the study group.

Of the 695 people in the study cohort, 43.9% were female. They were born from March 1956 to April 1992 and were ages 5.1 to 40.1 years at the first screen and 12.8 to 49.5 years on follow-up. The follow-up interval ranged from 0.5 to 13.6 years, with a median (interquartile range) of 11.6 (10.4–12.1) years, and a total period of 7666 years. Eight people started renal replacement therapy before the censor date, and lacking other interim measures, terminal values of ACR and eGFR were imputed for them on the date they started renal replacement therapy, as described in the Methods.

[Table 1](#) shows characteristics of the cohort at the first screen and at follow-up. The cohort was relatively

youthful at the first screen. At follow-up, when 619 people (89%) were adults (18+ years), levels of weight, BMI, and blood pressure were modest by western standards. The high rates of a PSGN history, high levels of C-reactive protein, and high rates of diabetes and dysglycemia are all remarkable, as described previously.<sup>11,15,16</sup> Urine ACR levels were generally higher in female than male individuals and were higher at follow-up than on the first screen: by the second screen only 50% of female and 66% of male individuals had ACR levels below the “microalbuminuria” threshold of 3.4 mg/mmol. Mean eGFR was modest, with a wide variance.

Birthweights, as shown in [Figure 1](#) and [Table 2](#), ranged from 1.07 kg to 4.64 kg, with a mean (SD) of 2.794 kg (0.52), which was 1 SD below current Australia-wide reference birthweights: 28.2% of subjects were low birthweight (<2.5 kg), compared with 6.2% of the 2013 Australian reference population.<sup>17</sup> Average birthweights were lower in older participants, with the prevalence of low birthweight (<2.5 kg) in those 30 to <40 years old (36.9%) twice that of the youngest persons (18.7%). Only 3 people had been “high”-birthweight infants (>4500 g). Birthweights in female individuals were somewhat lower than in male individuals, and the percent low birthweight was higher.

**Table 1.** Characteristics of the study cohort at first screen and at follow-up

|   | Female, n = 305, 43.9%   |                           | Male, n = 390, 56.1% |                    |
|---|--------------------------|---------------------------|----------------------|--------------------|
|   | First screen             | Follow-up                 | First screen         | Follow-up          |
| Age, yr                                     | 18.9 (10.1)              | 29.9 (10.0)               | 18.4 (9.0)           | 29.5 (9.1)         |
| Height, cm                                  | 152.9 (15.5)             | 160.1 (5.7)               | 161.4 (16.9)         | 171.1 (6.7)        |
| Weight, kg                                  | 53.1 (20.5)              | 65.4 (17.2)               | 53.9 (19.6)          | 64.5 (15.8)        |
| BMI, kg/m <sup>2</sup>                      | 21.9 (6.5)               | 25.5 (6.5)                | 19.9 (4.8)           | 22.0 (4.8)         |
| SBP, mm Hg                                  | 110.8 (13.2)             | 116.0 (16.4)              | 118.2 (14.8)         | 118.4 (15.6)       |
| DBP, mm Hg                                  | 65.6 (11.9)              | 74.7 (11.6)               | 70.7 (12.4)          | 74.8 (11.8)        |
| Past history of PSGN                        | 17.7%                    | 24.9%                     | 13.6%                | 21.3%              |
| BMI ≥25 kg/m <sup>2</sup> , ≥18 y           | 43.9%                    | 47.1%                     | 22.2%                | 21.5%              |
| Chol, mmol/l, ≥18 y                         | 4.2 (0.9)                | 4.5 (1.0)                 | 4.7 (1.0)            | 5.0 (1.0)          |
| HDL, chol mmol/l, ≥18 y                     | 1.1 (0.2)                | 1.3 (0.3)                 | 1.2 (0.2)            | 1.3 (0.3)          |
| TGs, mmol/l, <sup>d</sup> ≥18+ y            | 1.4 (1.0–2.1)            | 1.4 (1.0–2.4)             | 1.6 (1.2–2.3)        | 1.3 (0.9–1.9)      |
| CRP, mg/l, <sup>d</sup> ≥18 y               | 7.7 (3.1–14.4) (4.2–5.5) | 8.0 (3.0–13.0)            | 3.6 (1.7–7.2)        | 5 (2.0–7.0)        |
| HbA1c %, <sup>d</sup> ≥18 y                 | Not done                 | 5.8 (5.6–6.1)             | Not done             | 5.7 (5.5–5.9)      |
| Diabetes, ≥18 y                             | 10.9%                    | 20.6%                     | 3.3%                 | 9.3%               |
| ACR, mg/mmol <sup>d</sup>                   | 1.1 (0.6–5.0)            | 3.5 (1.1–21.8)            | 0.8 (0.5–1.9)        | 1.5 (0.7–5.8) 3.2) |
| ACR <3.4 mg/mmol                            | 71.2%                    | 49.5%                     | 81.5%                | 66.2%              |
| ACR 3.4–<34 mg/mmol                         | 18.4 %                   | 30.5%                     | 14.9%                | 25.4%              |
| ACR ≥34 mg/mmol                             | 10.5 %                   | 20.0%                     | 3.6%                 | 8.5%               |
| eGFR, ml/min per 1.73m <sup>2</sup> ≥18 yr  | 98.2 (24.1)              | 112.2 (33.8)<br>(34) (34) | 94.0 (16.1)          | 102.4 (19.5)       |
| eGFR <30 ml/min/1.73m <sup>2</sup> , ≥18 yr | 1.4%                     | 3.4%                      | 0.6%                 | 0.9%               |

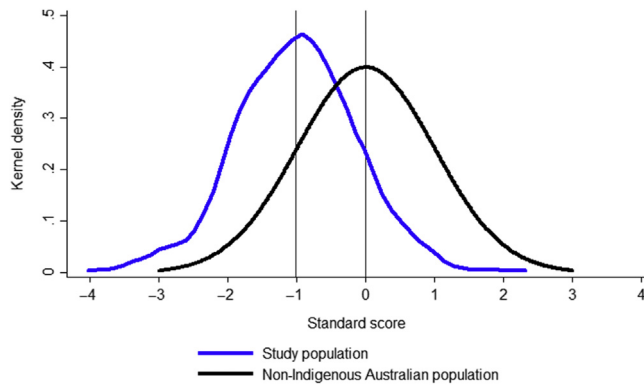
ACR, urine albumin creatinine ratio; BMI, body mass index; CRP, C-reactive protein; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL chol, high-density lipoprotein cholesterol; ns, not significant; PSGN, poststreptococcal glomerulonephritis; SBP, systolic blood pressure; TG, triglycerides.

<sup>a</sup><0.001,

<sup>b</sup><0.05, and

<sup>c</sup><0.01 denote the *P* values for difference between screens by sex, with paired *t*-tests for continuous data and 2-sample proportion tests for categorical data.

All summary statistics are mean (SD) unless specified <sup>d</sup>, which are median (interquartile range).



**Figure 1.** Birthweights in the study population versus the 2013 Australian population. Note: Study birth weights, N = 695, mean = 2.79 kg, SD = 0.52; nonindigenous Australian reference birth weights,<sup>18</sup> 2011, N = 283,996, mean = 3.375 kg, SD = 0.58.

**Prevalence of Renal Markers by Birthweight**

On the first screen, there was an inverse relationship between log<sub>2</sub> ACR and birthweight as continuous variables (P = 0.007), but it was not significant adjusted for age and sex (P = 0.783). Figure 2a shows the association by birthweight category, which was not significant for trend in either sex. On follow-up, log<sub>2</sub> ACR levels were inversely and significantly correlated with birthweight as a continuous variable (P < 0.001, unadjusted, P = 0.109 adjusted for age and sex). Figure 2b shows the relationships with birthweight category, which were significant in both female (P = 0.006) and male individuals (P = 0.001).

On first screen, eGFR was not correlated with birthweight on a continuum in persons age 18+ years at first screen (P = 0.225 adjusted for age and sex). Likewise, there was no association of eGFR with birthweight categories in female (P = 0.305) or male individuals (P = 0.744), as shown in Figure 3a. On follow-up, eGFR was correlated with birthweight on a continuum in persons age 18+ years when unadjusted (P = 0.017) but not when adjusted (P = 0.302). By birthweight categories, there was an association of eGFR in both female (P = 0.007) and male individuals (P = 0.012), as shown in Figure 3b.

**Changes in Albuminuria and eGFR Over Time (Progression and Incidence)**

The progression of albuminuria over time was inversely and significantly correlated with birthweight when unadjusted (P = 0.003), but not when adjusted for age and sex (P = 0.149). However, the trend by birthweight categories, shown in Figure 4a, was significant in both sexes (P = 0.011 for female and P = 0.031 for male individuals).

The proportion of persons with incident albuminuria, at or above the microalbuminuria threshold, was inversely and significantly correlated with birthweight overall (P = 0.019 adjusted for age and sex). By birthweight category, shown in Figure 4b, the relationship was significant for both female individuals, with P = 0.029, and for male individuals, P=0.030.

Changes in eGFR over time were not significantly correlated with birthweight as a continuous variable in either sex. Female individuals of the highest birthweight category appeared to have a net increase in eGFR over time (Figure 5a), and lower probability of substantial loss of eGFR over time, (Figure 5b), but none of these was significant.

**Amplification Phenomena**

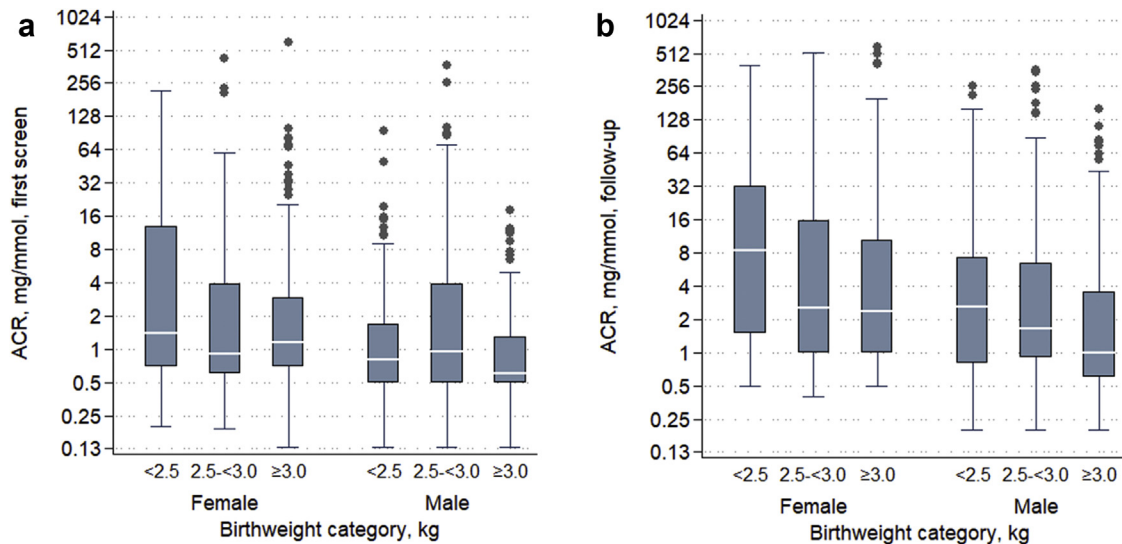
The association of albuminuria with lower birthweights was amplified in the presence of other risk factors, as shown in Figures 6 and 7. The additional “risk factors” used to demonstrate this phenomenon are a history of PSGN and a BMI above the group median. For these figures, data from both genders are combined, because numbers in some subgroups were small. Figure 6a demonstrates this phenomenon in changes in ACR levels over time (progression), and Figure 6b shows its expression in ACR levels at follow-up (prevalence). It is also expressed in the mean proportion of persons who had reached or exceeded various definitions of “pathologic albuminuria” by follow-up, including development of microalbuminuria and beyond (ACR ≥3.4), shown in Figure 7a, and “overt” or macroalbuminuria (ACR ≥34), shown in Figure 7b. The associations of PSGN or higher range BMIs with elevated levels of ACR were minimized in

**Table 2.** Birthweights of participants in study cohort by gender and age at first screen

| Age at first screen, yr | Female individuals |                |                    | Male individuals |                |                    |
|-------------------------|--------------------|----------------|--------------------|------------------|----------------|--------------------|
|                         | n                  | Bwt, mean (SD) | Low Bwt <2.5 kg, % | n                | Bwt, mean (SD) | Low Bwt <2.5 kg, % |
| 5-<10                   | 83                 | 2.818 (0.49)   | 25.3               | 88               | 3.015 (0.54)   | 12.5               |
| 10-<20                  | 81                 | 2.752 (0.50)   | 27.2               | 134              | 2.829 (0.55)   | 25.4               |
| 20-<30                  | 84                 | 2.745 (0.55)   | 38.1               | 114              | 2.685 (0.51)   | 34.2               |
| 30-<41                  | 57                 | 2.664 (0.50)   | 49.1               | 54               | 2.724 (0.37)   | 24.1               |
| All, 5-<41 yr           | 305                | 2.752 (0.52)   | 33.8               | 390              | 2.814 (0.53)   | 24.9               |

Bwt, birthweight in kg.

Tests for trend (nptrend and tabodds, respectively) in female individuals: bwt, kg P = 0.047, low bwt P = 0.0015; in male individuals: bwt, kg P < 0.001, low bwt P = 0.0133.



**Figure 2.** Albumin creatine ratio (ACR) by birthweight category and sex at (a) first screen, and (b) follow-up. Note: (a) *P* for trend = 0.207 for females, and = 0.128 for males; (b) *P* for trend = 0.006 for females, and = 0.001 for males.

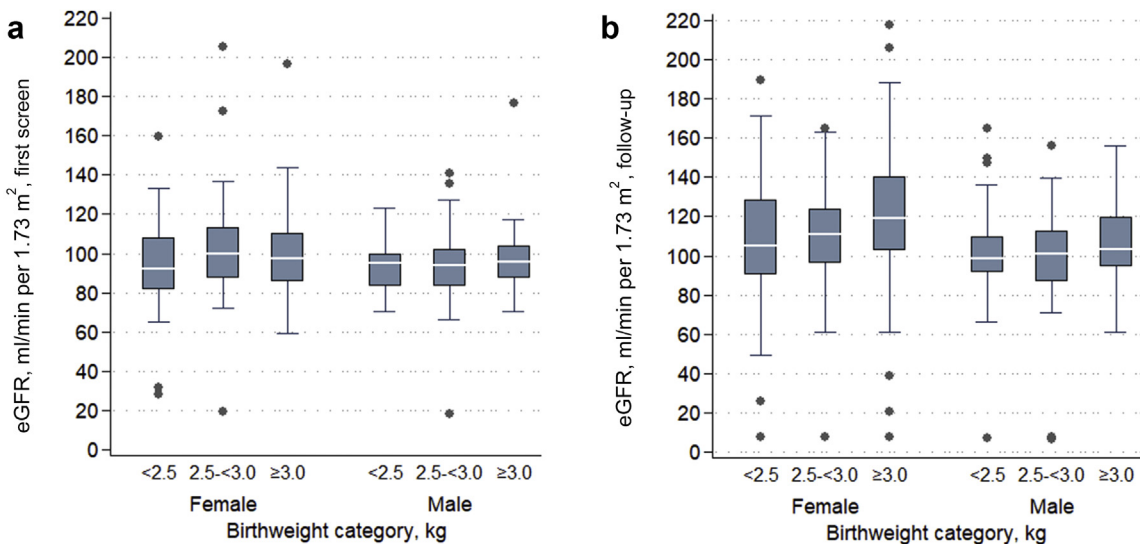
persons of more robust birthweight; conversely, associations of lower birthweights with albuminuria were amplified in the presence of higher BMIs and a history of PSGN.

**Relationships of eGFR to ACR**

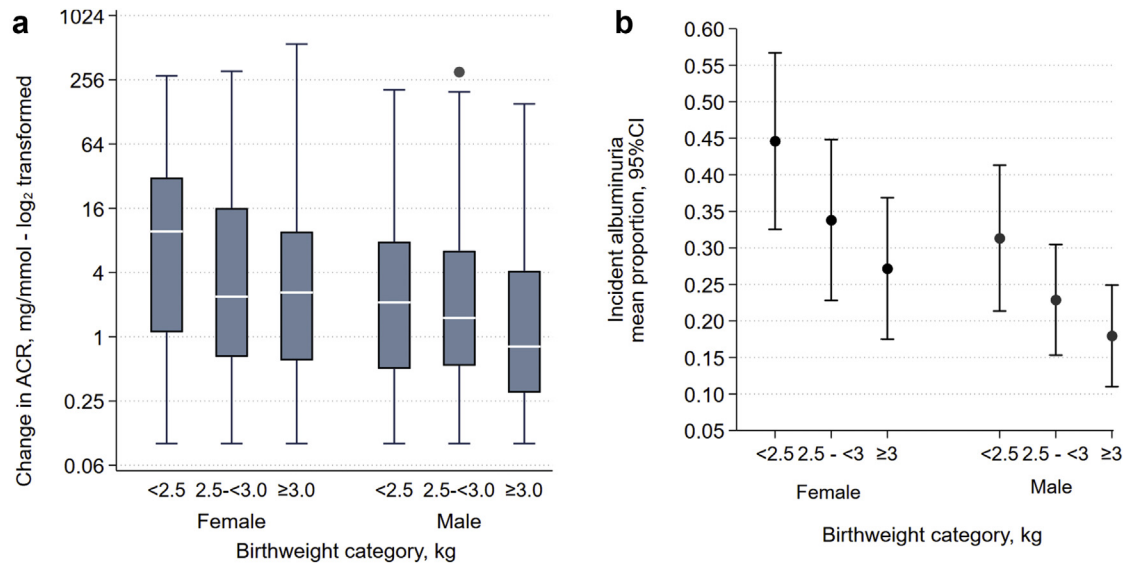
At both screens, there were close relationships between eGFR and ACR. As shown in Figure 8a–c, there was an inverse relationship between eGFR and log<sub>2</sub> ACR over a continuum in male individuals at the first screen, beyond a threshold level in the early-mid “micro-albuminuria” range in female individuals on the first screen, and in both sexes on follow-up. In female individuals at both screens, and arguably in male individuals on the second screen, this was preceded by

an increase in eGFR with higher ACR levels within the “normal” range. Figure 8c indicates an inverse relationship between the changes in ACR and eGFR beyond an ACR increase of approximately 16 to 64 g/g between the screens, again, more marked in female individuals.

Table 3 shows the data from 3 sets of multivariable equations examining correlations of specific risk factors, including birthweight, with both prevalent and incident albuminuria, in people aged ≥18 years, with adjustment for other significant factors. Older age, female sex, high BMI, and PSGN history correlated significantly with most expressions of albuminuria. Higher C-reactive proteins also independently marked prevalence, progression, and incidence of albuminuria (not shown). Higher HbA1c was also significant, but



**Figure 3.** eGFR in adults by birthweight and sex at (a) first screen and (b) follow-up. Note: (a) *P* for trend = 0.305 female, = 0.744 male; (b) *P* for trend = 0.007 for females, and = 0.012 for males; one eGFR value (244) not graphed. eGFR= estimated glomerular filtration rate; adults are ≥18 years.



**Figure 4.** (a) Change in albumin creatinine ratio (ACR) by birthweight category and sex; (b) incident albuminuria by birthweight category and sex. Note: (a)  $P$  for trend = 0.011 female, = 0.031 male; (b)  $P$  for trend = 0.029 female, = 0.030 male. Incident albuminuria = ACR <3.4 mg/mmol at first screen and  $\geq$ 3.4 mg/mmol at follow-up. CI = confidence interval.

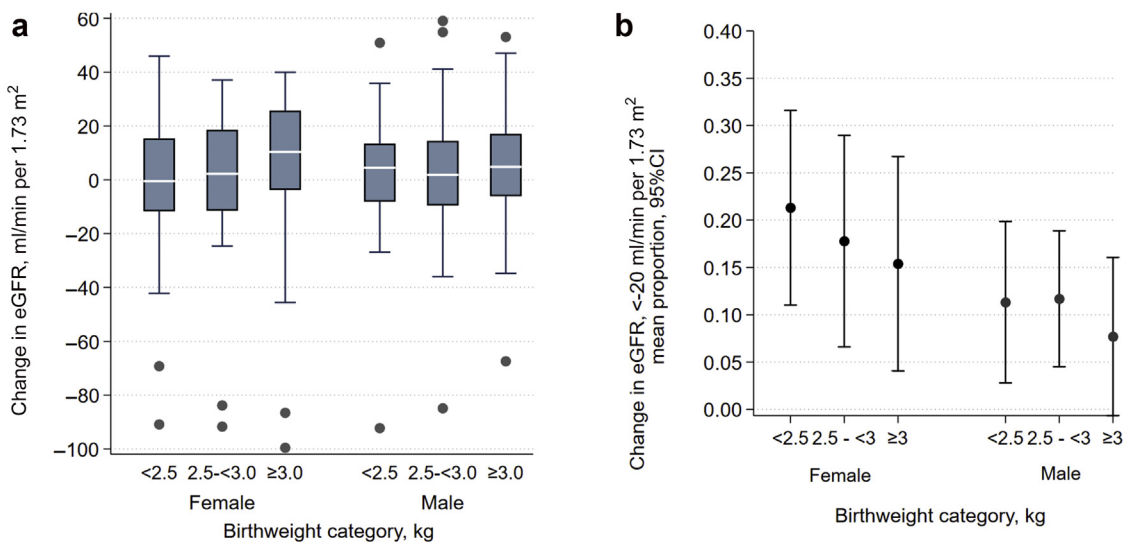
only when BMI was omitted from the models. Relative to people with birthweights of  $\geq$ 3 kg, persons of lower birthweight had higher odds ratios for prevalent and incident albuminuria. The models predict, per kg of higher birthweight, 21% and 41% reductions in the prevalence of albuminuria at the first and follow-up screens, respectively, and a 51% reduction in incident albuminuria ( $\geq$ 3.4 mg/mmol) between screens.

## DISCUSSION

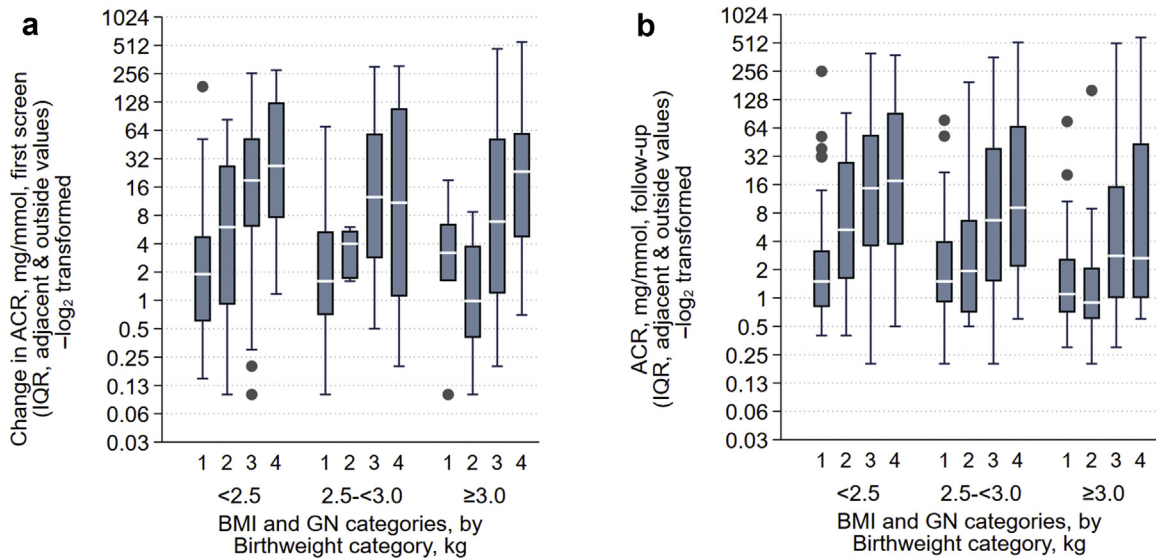
This study confirms that levels of albuminuria were inversely correlated with birthweight.<sup>9,10</sup> The

associations of albuminuria with lower birthweights at follow-up were stronger than the associations at baseline, showing that the phenomenon was *magnified over time*. The proportions of persons whose ACR rose between examinations from “normal” to “microalbuminuria” levels and above, were also higher in persons of lower birthweight.

The magnitude of the effects of birthweight on changes in ACR over time was not trivial. For persons with ACR <3.4 at the first screen, the mean change in ACR between screens was 4.3 (95% confidence interval 2.2–6.4) for those of birthweights  $\geq$ 3.0 kg and was 8.4 (95% confidence interval 5.0–11.7) mg/mmol for those



**Figure 5.** (a) Change in estimated glomerular filtration rate (eGFR) in adults by birthweight category and sex. (b) Change in eGFR of more than 20 ml/min per 1.73 m<sup>2</sup> by birthweight category and sex. Note: (a)  $P$  for trend = 0.272 for females, and = 0.411 for males; (b)  $P$  for trend = 0.450 for females, and = 0.609 for males. Adults are  $\geq$ 18 years at first screen; 3 eGFR delta values < -119 not graphed in (a). CI = confidence interval.

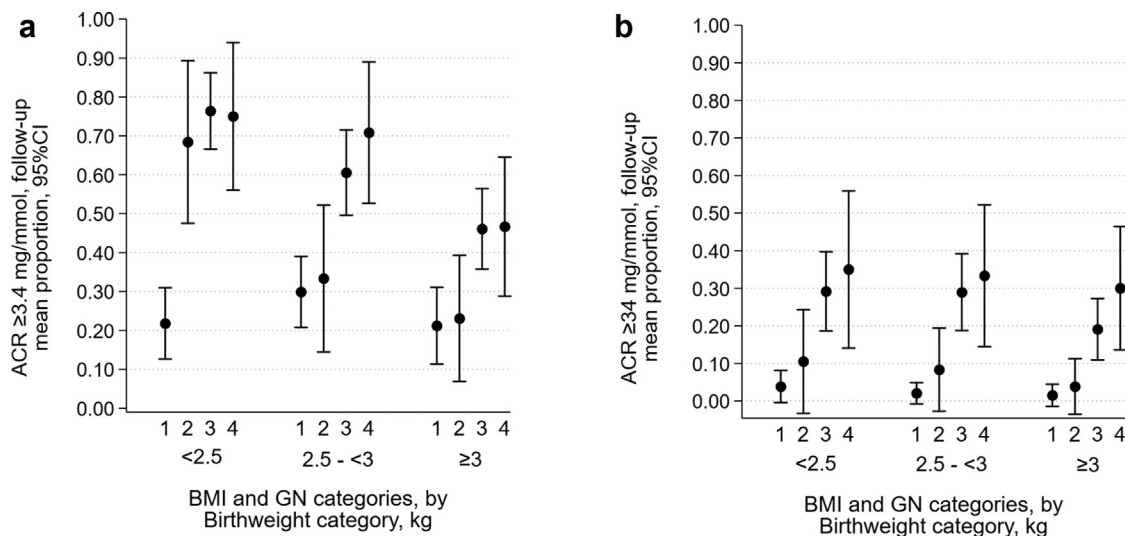


**Figure 6.** Albumin creatinine ratio (ACR) parameters in adults by birthweight category, body mass index (BMI) median, and poststreptococcal glomerulonephritis (PSGN) categories: (a) change in ACR in participants who were adults at first screen; (b) ACR in adults at follow-up. Note: (a) *P* for trend across each birthweight category: <0.001 (<2.5), <0.001 (2.5 to <3), 0.015 (≥3); (b) *P* for trend across each birthweight category: <0.001 (<2.5), <0.001 (2.5 to <3), 0.001 (≥3). BMI and PSGN categories: 1 = low BMI and no PSGN history; 2 = low BMI and PSGN history; 3 = high BMI and no PSGN history; 4 = high BMI and PSGN history. Adults are ≥18 years; BMI Yes = BMI ≥ adult median of 21.8 kg/m at follow-up; PSGN = history of PSGN, Yes/No. IQR = interquartile range.

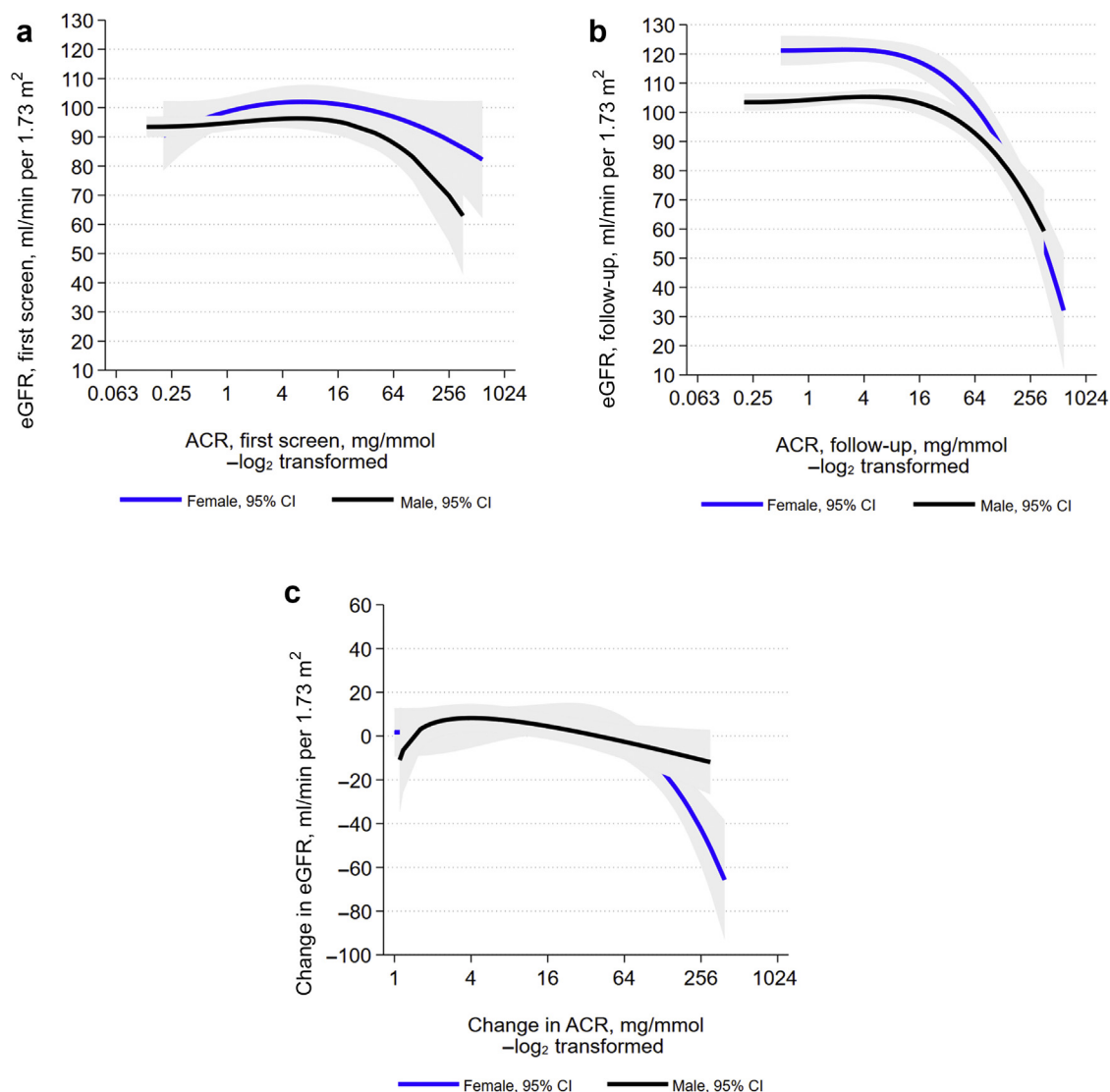
of birthweights <2.5, while the proportions who developed ACR ≥3.4 were 21% (95% confidence interval 17%–28%) and 37% (95% confidence interval 30%–45%), respectively.

The associations of lower birthweights with albuminuria and its progression were amplified in the presence of other risk factors: illustrated here as a

higher BMI and a history of PSGN.<sup>3,11</sup> The associations with birthweight were maximized when both additional risk factors were present and minimized when neither was present. This is compatible with a multideterminant model of albuminuria in which lower birthweights are among several initiating or facilitating factors. Adult weight, waist



**Figure 7.** Albuminuria parameters in adults at follow-up by birthweight category and body mass index (BMI) median and poststreptococcal glomerulonephritis (PSGN) categories: (a) urine albumin creatinine ratio (ACR) ≥ the microalbuminuria threshold; (b) urine ACR ≥ the overt albuminuria threshold. Note: (a) *P* for birthweight category trend: <0.0001 (<2.5), <0.0001 (2.5 to <3), 0.0009 (≥3). (b) *P* for birthweight category trend: <0.0001 (<2.5), <0.0001 (2.5 to <3), <0.0001 (≥3). BMI and PSGN categories: 1 = low BMI and no PSGN history; 2 = low BMI and PSGN history; 3 = high BMI and no PSGN history; 4 = high BMI and PSGN history. Adults are ≥18 years; ACR microalbuminuria threshold = 3.4 mg/mmol; ACR overt albuminuria threshold = 34 mg/mmol; BMI Yes = BMI ≥ adult median of 21.8 kg/m<sup>2</sup> at follow-up; PSGN = history of PSGN, Yes/No. CI = confidence interval.



**Figure 8.** Estimated glomerular filtration rate (eGFR) in adults by albumin creatine ratio (ACR) and sex: (a) at first screen; (b) at follow-up; (c) change in ACR over change in eGFR. Note: (a)  $P$  for model: = 0.891 for females, and = 0.122 for males; (b)  $P$  for model: =  $\leq 0.001$  for females, and =  $\leq 0.001$  for males; (c)  $P$  for model =  $< 0.001$  for females, and = 0.153 for males. Adults are  $\geq 18$  years at first screen; fractional polynomial models fitted; ACR delta values are  $\geq 1.0$ . CI = confidence interval.

circumference and waist hip ratios, HbA1c levels, and rates of diabetes on follow-up have a similar amplifying effect to BMI: other factors with similar magnifying effects on ACR were higher levels of C-reactive protein, the presence of scabies, numbers of skin sores,<sup>3</sup> high titers of antibodies against *Helicobacter pylori*, and, in women, grand multiparity ( $\geq 3$  deliveries) (all unpublished). There are undoubtedly many other amplifying factors, for example, in a cross-sectional study in another remote-living Aboriginal group in the Northern Territory, total immunoglobulin levels, von Willebrand Factor, and cytomegalovirus antibody titer were also significantly correlated with ACR.<sup>18,19</sup> In addition, we cannot exclude a genetic contribution to renal disease risk, which is still under study in this population.<sup>20,21</sup>

The average birthweight (3.332 kg) for persons in the highest category of birthweight ( $\geq 3$  kg) in this study was close to that of the Australian nonindigenous population, which is currently a mean/median of 3.35 kg.<sup>22</sup> Birthweights  $\geq 3$  kg were substantially protective against both prevalent and incident albuminuria. The protective effect was evident among those who were not overweight and did not have PSGN and applied to some extent in the higher ranges of albuminuria associated with high BMIs or past episodes of PSGN.

Thus, lower birthweights have made a substantial contribution to the high rates of renal disease and renal failure in this remote-living Australian Aboriginal group. However, there was a trend of improving birthweights in this community between the mid-1950s and the mid-1990s (Table 2), which promises mitigation



**Table 3.** Odds ratios (95% CI) for prevalence of albuminuria at the first screen, prevalence of albuminuria at follow-up and development of incident albuminuria between screens, associated with a variety of risk factors, derived from multivariable analyses, and adjusted for the other specified significant risk factors

| Model parameters     | First screen ACR $\geq 3.4$ ,<br>age $\geq 18$ at first screen<br>136/336 | Follow-up ACR $\geq 3.4$ ,<br>age $\geq 18$ at follow-up<br>273/619 | Incident ACR $\geq 3.4$ ,<br>age $\geq 18$ at follow-up<br>between exams, 137/464 |
|----------------------|---|---|---|
| Age, per y           | 1.08 (1.03–1.13), $P = 0.002$   | 1.10 (1.07–1.13), $P < 0.001$                                       | 1.07 (1.04–1.09), $P < 0.001$   |
| Female               | 1.68 (1.03–2.73), $P = 0.037$   | 1.60 (1.09–2.35), $P = 0.018$                                       | 1.36 (0.86–2.14), $P = 0.187$   |
| BMI $\geq$ median    | 3.44 (2.11–5.62), $P < 0.001$   | 2.69 (1.82–3.97), $P < 0.001$                                       | 2.67 (1.67–4.24), $P < 0.001$   |
| PSGN history, Y/N    | 2.48 (1.34–4.62), $P = 0.004$   | 2.12 (1.38–3.27), $P = 0.001$                                       | 1.60 (0.94–2.70), $P = 0.082$   |
| Bwt $\geq 3$ kg      | Referent  | Referent  | Referent  |
| Bwt 2.5–<3 kg        | 2.13 (1.13–4.01), $P = 0.019$   | 1.45 (0.92–2.28), $P = 0.109$                                       | 1.53 (0.89–2.64), $P = 0.127$   |
| Bwt <2.5 kg          | 1.75 (0.93–3.30), $P = 0.083$   | 1.83 (1.14–2.94), $P = 0.013$                                       | 2.19 (1.27–3.79), $P = 0.005$   |
| Bwt, kg <sup>a</sup> | 0.79 (0.48–1.27), $P = 0.328$   | 0.59 (0.41–0.85), $P = 0.005$                                       | 0.49 (0.33–0.76), $P = 0.001$   |

ACR, urine albumin creatinine ratio, mg/mmol; BMI, body mass index, kg/m<sup>2</sup>, first screen adult BMI median = 22.2 kg/m<sup>2</sup>, incident and follow-up adult BMI median = 21.8 kg/m<sup>2</sup>; Bwt, birthweight; CI, confidence interval; PSGN, poststreptococcal glomerulonephritis; Regression output as odds ratio (95% CI),  $P$  value.

<sup>a</sup>Birthweight in kg is substituted for categories of birthweight.

of risk from this source. It also predicts a reduction in nonrenal deaths, which both lower birthweights and albuminuria predict, if other risk factors can be contained.<sup>4,8</sup>

In fact, we have already demonstrated improvement in health profiles in this community through a matched-pair study of participants in the first and second community-wide screens in this same setting.<sup>23</sup> The ongoing challenge is to lessen all risk factors of significance; highly visible among these are high rates of smoking, exposure to other drugs, excessive drinking, obesity, substandard living conditions, poor diet,<sup>24,25</sup> and widespread prenatal alcohol exposure.<sup>26</sup>

Lower birthweights might influence kidney disease risk and progression through several mechanisms. A suboptimal intrauterine environment results in lower nephron endowment<sup>27,28</sup> and nephron development is impaired with prematurity, which commonly accompanies lower birthweights.<sup>27–32</sup> Moreover, reduced or frankly “impaired” postnatal kidney hypertrophy is widely documented in low birthweight infants and children.<sup>33,34</sup> In our dataset, the failure of eGFR in low birthweight persons to increase between the 2 examinations, despite increasing age and body mass increase, might reflect restriction of the kidney hypertrophy that usually accompanies advancement into adult life.

Of course, renal disease does not exist in isolation,<sup>35,36</sup> lower birthweight is not the sole risk factor for renal disease and lower birthweights have broader effects beyond renal disease. In children in this same community, birthweight correlated directly with weight, height, waist, hips, and kidney volume, and inversely with waist/hip ratio,<sup>37</sup> whereas in young adults, low birthweights were also associated with higher blood pressures,<sup>38,39</sup> smaller kidneys,<sup>39</sup> higher urine ACRs,<sup>9,10</sup> and a greater number of more morbid cardiovascular events.<sup>40,41</sup> Lower birthweights were

also associated with excess all-cause natural deaths in infants, children, and young and middle-aged adults; this phenomenon was most marked for pulmonary deaths (an 8-fold increase in young adults of low birthweight), but renal and cardiovascular deaths were approximately doubled as well.<sup>42,43</sup>

These findings are undoubtedly generalizable to remotely situated Aboriginal communities in the Northern Territory and across Australia more broadly.<sup>36,44,45</sup> The great excess of kidney failure in adults in these settings probably reflects, in part, dramatic reductions in infant mortality in the past 60 years, especially among infants of low birthweights, as well as reduced competing mortality in adults due to delay or prevention of infectious deaths and better management of chronic lung disease and cardiovascular risk. Thus, more people with albuminuria are surviving long enough to progress to terminal kidney failure. We have described these phenomena elsewhere and note that they are echoed in many populations across the world that are undergoing rapid epidemiologic transition.<sup>32,34,35,43,45</sup>

This study extends knowledge from the association of birthweight with prevalent albuminuria, to its influence on incident albuminuria and progression of kidney disease. Prevalence studies are limited in their ability to expose such associations by prior culling of people who have already developed renal failure; here that source of underascertainment was minimized through knowledge of the fate of all participants in the original screen and imputation of terminal ACR and eGFR values for those who had developed renal failure before the second screen. The findings in this study also support our earlier observations of the associations of ACR with other risk factors, the reciprocity of ACR and eGFR, and the multideterminant (vs single cause) origins of albuminuria.<sup>3,12</sup>

Many findings in the “eGFR” study in a cohort of Indigenous adults from multiple remote sites across the Northern Territory and Queensland are compatible with ours.<sup>46-51</sup> They confirm the centrality of albuminuria as the kidney disease marker, and the later loss of eGFR over time, which is predicted by baseline ACR. Of interest, the “eGFR study” also shows higher prevalence of kidney disease in persons of greater socioeconomic disadvantage.<sup>51</sup> Birthweight and PSGN history were not recorded in the eGFR study, but low birthweight and PSGN are probably some of the drivers of that association.

### This Study Has Considerable Methodological and Conceptual Strengths

The broader program in which this study is embedded is unparalleled among research ventures among remote-living Aboriginal people in Australia: more than 80% of the age-eligible population of the target groups have participated in each stage, and outcomes have been documented from all available sources. The data on progression and new incident disease are novel, and the numbers are robust.

### Limitations of the Study

The lack of follow-up values on 135 persons is unavoidable, reflecting community events, their accentuated mortality, and the obligations and priorities of community members. The imputation of terminal ACR and eGFR values to people if they started dialysis between the conduct of the measurement intervals, has enriched the study cohort with people with serious renal disease. This, however, does not compromise the conclusion of the associations of birthweight within the study group. We can only speculate about other factors that have influenced health profiles. Poor nutrition is a strong candidate, and store sales audits indicate little improvement over the past few decades.<sup>24,25</sup> Health services have improved<sup>52,53</sup> and have included systematic offering of angiotensin-converting enzyme inhibitors to people with albuminuria and/or hypertension, since the late 1990s.<sup>6</sup> Members of our study cohort were offered treatment when they qualified for it, either at baseline examination or during follow-up. On the follow-up examination, at least 110 of the cohort (15.5%) were prescribed angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and at least 64 (9%) were prescribed glucose-lowering treatments for diabetes. If those treatments had the desired effects, they would have blunted increases in ACR and decreases in eGFR in at-risk persons, and minimized differences between low birthweight and normal birth weight persons, at

follow-up screen. However, such differences were stronger in the second than the first screen.

These findings enhance our understanding of the pathophysiology of kidney disease, and through the common marker of albuminuria, cardiovascular disease, in high-risk populations. They encourage expectations of lower disease rates as specific risk factors are contained. They underscore the importance of ongoing efforts to improve pregnancy outcomes, and to reduce the density of risk factors in these environments. The importance of PSGN as a risk factor supports arguments for development of a vaccine against group A streptococci: this has long been advocated for prevention of rheumatic heart disease but is equally indicated for renal protection. Finally, the findings provide a rationale for more regular surveillance for people of lower birthweights, and greater readiness to start renal protective treatment. The potential for pharmacologic prevention or delay of onset of albuminuria, diabetes, and hypertension in this population looks promising for people with currently “normal” renal function that remains unresolved.<sup>54</sup>

### DISCLOSURE

All authors declare no competing interests.

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### SUPPLEMENTARY MATERIAL

[Supplementary File \(PDF\)](#)

**Table S1.** The birthweight study cohort and persons without follow-up observations.

**STROBE Statement.**

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