The influence of birthweight, past poststreptococcal glomerulonephritis and current body mass index on levels of albuminuria in young adults: the multideterminant model of renal disease in a remote Australian Aboriginal population with high rates of renal disease and renal failure

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ABSTRACT

Background. Australian Aborigines in remote areas have very high rates of kidney disease, which is marked by albuminuria. We describe a ‘multihit’ model of albuminuria in young adults in one remote Aboriginal community.

Methods. Urinary albumin/creatinine ratios (ACRs) were measured in 655 subjects aged 15–39 years and evaluated in the context of birthweights, a history of ‘remote’ poststreptococcal glomerulonephritis (PSGN; ≥5 years earlier) and current body mass index (BMI). Birthweight had been <2.5 kg (low birthweight, LBW) in 25.4% of subjects and 22.8% had a remote history of PSGN.

Results. ACR levels rose with age. It exceeded the microalbuminuria threshold in 33.6% of subjects overall (25% of males and 45% of females). In multivariate models, birthweight (inverse-ly), remote PSGN and current BMI were all independent predictors of ACR levels. The effects of birthweight and PSGN and their combination were expressed through amplification of ACR levels in relation to age and around the group median BMI of 20.8 kg/m². In people with BMI <20.8 (low birthweight, LBW) in 25.4% of subjects and 22.8% had a remote history of PSGN.

Conclusion. Much of the great excess of disease in this population is explained by high rates of the early life risk factors, LBW and PSGN. Their effects are expressed through amplification of ACR in the context of increasing age and are further moderated by levels of current body size. Both early life risk factors are potentially modifiable.

Keywords: Australian Aborigines, low birthweight, chronic kidney disease, multideterminant model, poststreptococcal glomerulonephritis

INTRODUCTION

The causes of the high rates of kidney disease (chronic kidney disease, CKD) and kidney failure in remote-living Aboriginal people are not entirely understood. We have proposed that the epidemic of chronic disease generally and CKD specifically is related to their rapid and recent epidemiologic and health transitions, in the context of changes in living conditions and striking reductions in infant mortality since the 1960s [1–3].

Kidney disease is marked by albuminuria, which antecedes all renal failure and also predicts diabetes and most of the risk for cardiovascular disease, which is greatly increased [4–8]. Multivariate modelling shows albumin/creatinine ratio (ACR) levels are multideterminant, rather than determined by a single cause or agent [4], compatible with the ‘multihit’ hypothesis for kidney disease proposed by Nenov and colleagues [9].
Constitutional, inflammatory and metabolic markers, which are significantly correlated with albuminuria include age, female gender, body mass index (BMI), diabetes, levels of glycaemia more generally, skin sores and scabies, high titre antibodies against Helicobacter pylori, levels of C-reactive protein and inversely, levels of HDL-c [4, 10]. We have also described the association of albuminuria with birthweights (versus) and with a previous poststreptococcal glomerulonephritis (PSGN) history [11–13].

Our early analyses of birthweight effects were limited by the low numbers and relative youthfulness of participants, because systematic recording of birthweights did not begin until the late 1960s. However, with the passage of time leading up to the current analysis, the numbers of adults with recorded birthweights has tripled, and the maximum age of those with recorded birthweights has increased by a decade. Most subjects whose records for PSGN are likely to be reliable [14], now have available birthweights.

This article describes relationships of ACR to birthweight, PSGN and current BMI in a cohort of young adults, with all those parameters documented, in that same community.

MATERIALS AND METHODS

Subjects in this study were members of a remote Aboriginal community who participated in one or both community-wide health screens performed in 1992–1996 and in 2004–2006, and in whom birthweights and good quality medical records (for a history of PSGN) were available. More than 80% of the age-eligible people, except for pregnant and menstruating females and people who were hospitalized or on dialysis, participated in each screen.

Assessments at screening included ACRs measured on random urine samples. Estimated glomerular filtration rate (eGFR) was calculated by the shortened Modification of Diet in Renal Disease (MDRD) formula [15]. Values from the most recent survey for each individual were used in this analysis. Medical records were reviewed for birthweight and for past episodes of acute PSGN. The first record of birthweight in this community was in 1956, and birthweights were recorded with some regularity from the mid-1960s onwards [12, 13]. Recording of PSGN seems good in clinical records after the late 1960s, perhaps following the arrival of the Northern Territory’s first paediatrician, Dr Alan Walker, in 1964. As previously described in detail, a PSGN diagnosis was based on a compatible clinical picture, defined by urine abnormalities, accompanied by oedema and/or hypertension and/or compatible serologic changes, which included elevated levels of anti-streptococcal antibodies and low levels of total haemolytic complement and/or C3 [14].

Age at diagnosis of the PSGN episode and the time elapsed since that diagnosis was calculated. People were categorized as those without a PSGN history and those with history of PSGN that had occurred 5 or more years prior to screening (‘remote PSGN’). This limitation was imposed to eliminate potential contributions to urine findings of lingering acute inflammation from PSGN [14]. Patients with a PSGN history of <5 years prior to screening were to be excluded from the analysis: in fact, no person met this criterion. Levels of urine ACR were analysed in the context of age at screening, birthweight, PSGN history and current BMI.

Levels of urine ACR showed a skewed distribution, as shown in Figure 1a, and were analysed as a log2 transformed continuous variable (each unit representing stepwise doubling of the base value), resulting in data better approximating a normal distribution as shown in Figure 1b.

Birthweights were analysed as a continuous variable and around the traditional definition of low birthweight (LBW) of <2.5 kg. ACR levels were inspected in the context of current BMIs, around the group median BMI of 20.8 kg/m².

We explored suggestions of nonlinear relationships of log2 ACR and predictors from scatter plots by adding higher order-terms of predictor variables to regression models. Stata 12.1 statistical package (Stata Corporation, College Station, TX) was used for all analyses [16]. All P-values are two-tailed and statistical significance was calculated at the α = 0.05 level.

The project was approved by the Behavioural and Social Science Ethical Review Committee of the University of Queensland, the Human Research Ethics Committee of the Northern Territory Department of Health and Community Services and Menzies School of Health Research, and the community health board.

RESULTS

A total of 655 subjects who were ages 16 to <40 years at time of health screening had both recorded birthweights and an available medical record (for inspection for a PSGN history). Each participant’s screening information is represented only once. When a person participated in more than one community screen, age and data from the most recent screen were used.

Table 1 shows the characteristics of the study population. Especially noteworthy were the high rates of LBW <2.5 kg (22.8% of males and 28.9% of females) and very high rates of a remote PSGN history of 21.8% in males and 24.3% in females. All PSGN episodes occurred at least 5 years before screening, at average age of about 8 years, and about 20 years prior to testing. On average, BMIs were higher in females than males, with median values of 20.3 in males and 22.7 in females, which are
modest in relation to those described in non-indigenous Australians in the AUSDIAB study [17]. ACR levels were higher in females than males, and the prevalence of diabetes tended to be higher in females.

Table 2 shows that birthweight, PSGN and BMI all had independent significance in predicting log_{2}ACR in both males and females, and in the group in aggregate. There were significant interaction terms of birthweight and PSGN in both sexes (P = 0.02 in males; P = 0.01 in females).

Figures 2–4 confirm, in the aggregate group, that ACR in relation to age was amplified in the presence of LBW, with a PSGN history and with higher BMIs. These phenomena could also be demonstrated in terms of ACR categories, with the proportions with ‘normal’ levels of ACR lower, and the proportions with ‘overt’ levels of albuminuria higher in each high-risk category (not shown). The significance of those differences persists with adjustments for age and sex.

Figure 5 shows the amplification of ACR in the context of age in the presence of LBW and/or PSGN. ACR levels were lowest in those with normal birthweight and no PSGN, intermediate in those with either LBW or with PSGN and were highest in those with both LBW and with a PSGN history. Figure 6 demonstrates a similar gradation of ACR categories according to the risk factor groupings.

However, these relationships differ according to BMI. Figure 7 shows that, in people with BMIs less than the group median, there was a modest increase in ACR with age in those without LBW or PSGN, that there was not a significant further elevation of ACR with either LBW alone or with PSGN alone, but that the combination of LBW and PSGN was associated with a strikingly higher ACR across the age continuum. Figure 8 supports those findings in terms of ACR categories. Figure 9 shows that, among people with BMIs at or above the group median and without LBW or known PSGN, ACR levels rose significantly with age, were significantly elevated above those levels in the presence of either LBW or a PSGN history, and that further amplification around these already high ACR levels was not readily discernible. Analysis of ACR by categories, shown in Figure 10, supports those impressions.

### DISCUSSION

In young adults in this community, ACR levels, and their increase with age, were correlated with lower birthweights, childhood episodes of PSGN and with current BMI, and their effects were multiplicative. Lower BMIs were relatively protective against the ACR amplifying effects of LBW and PSGN, while higher BMIs had a sensitizing or exacerbating effect. The lowest ACRs and the most modest increases with age were in those with BMIs below the group median without LBW and with

#### Table 1. Characteristics of study subjects

<table>
<thead>
<tr>
<th>Term</th>
<th>Males (n = 377)</th>
<th>Females (n = 278)</th>
<th>All (n = 655)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>Mean (SD)</td>
<td>26.3 (6.9)</td>
<td>26.1 (6.8)</td>
</tr>
<tr>
<td>PSGN</td>
<td>n, %</td>
<td>82, 21.7%</td>
<td>68, 24.3%</td>
</tr>
<tr>
<td>Age at PSGN</td>
<td>Mean (SD)</td>
<td>7.3 (3.4)</td>
<td>8.6 (5.6)</td>
</tr>
<tr>
<td>Years since PSGN</td>
<td>Mean (SD)</td>
<td>19.1 (6.2)</td>
<td>17.9 (5.5)</td>
</tr>
<tr>
<td>Birthweight (kg)</td>
<td>Median (IQR)</td>
<td>2.8 (2.8–2.9)</td>
<td>2.8 (2.7–2.9)</td>
</tr>
<tr>
<td>Birthweight &lt;2.5 kg</td>
<td>n, %</td>
<td>86, 22.8%</td>
<td>81, 26.9%</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>Median (IQR)</td>
<td>20.3 (19.8–20.5)</td>
<td>22.6 (21.6–24.2)</td>
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<tr>
<td>BMI &gt;25 kg/m²</td>
<td>n, %</td>
<td>72, 19.1%</td>
<td>105, 37.5%</td>
</tr>
<tr>
<td>ACR* (g/mol)</td>
<td>gmean (95% CI)</td>
<td>1.6 (1.4–1.9)</td>
<td>4.1 (3.3–4.9)</td>
</tr>
<tr>
<td>ACR, &lt;3.4</td>
<td>n, %</td>
<td>282, 74.8%</td>
<td>154, 55.0%</td>
</tr>
<tr>
<td>ACR, 3.4–33</td>
<td>n, %</td>
<td>80, 21.2%</td>
<td>88, 31.4%</td>
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<tr>
<td>ACR, ≥34</td>
<td>n, %</td>
<td>15, 4.0%</td>
<td>38, 13.6%</td>
</tr>
<tr>
<td>GFR – MDRDb</td>
<td>Mean (SD)</td>
<td>109.0 (22.5)</td>
<td>121.8 (29.1)</td>
</tr>
<tr>
<td>Low GFR (&lt;60%)</td>
<td>n, %</td>
<td>1, 0.3%</td>
<td>5, 1.8%</td>
</tr>
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<td>SBP (mmHg)</td>
<td>Mean (SD)</td>
<td>116.9 (13.7)</td>
<td>111.6 (14.1)</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>Mean (SD)</td>
<td>72.1 (11.1)</td>
<td>71.3 (10.9)</td>
</tr>
<tr>
<td>BP ≥135/85</td>
<td>n, %</td>
<td>61, 16.2%</td>
<td>37, 13.2%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>n, %</td>
<td>16, 4.2%</td>
<td>29, 10.4%</td>
</tr>
</tbody>
</table>

*3.4 g/mol = 30 mg/g creatinine; 34 g/mol = 300 mg/g creatinine.
*3mL/min/1.73 m².
no PSGN history; in them, single risk factors had only a modest effect on ACR, but the combination of LBW plus PSGN produced significantly higher ACRs and more marked increases with age. In people with BMIs $\geq 20.8$ (the group median), who had significant age-related ACR increases, both LBW and PSGN separately produced striking further amplification, and around these high levels, further additive effects of both risk factors together were difficult to discern. This is probably because people with the highest ACRs had already been culled from that group by premature death and renal failure, both of which are predicted by elevated ACRs [5].

This is the first formal demonstration of the effects of multiple early life risk factors on albuminuria. The expression of these risk factors through amplification of ACR in the context

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**Figure 2:** Log(2) transformed ACR data ACR.

**Figure 3:** ACR by age and birthweight categories.

**Figure 4:** ACR by age and PSGN history.

**Figure 5:** ACR by age and BMI categories.

**Figure 6:** ACR by risk group.

**Figure 7:** ACR categories by risk group.
of adult BMI is also illuminating. It supports previous demonstrations in this community of the BMI dependency of proteinuria in marking serologic evidence of persistent streptococcal infection [17] and of exacerbation by higher BMIs of the effects of LBW on ACR elevation [4, 13]. These phenomena help explain why multivariate modelling has always shown that adult BMI or its surrogates account for most of the explained variance of ACR in this population, even though BMI levels are relatively modest relative to those in the Australian non-indigenous population [18].

These findings are compatible with the ‘multihit’ hypothesis of renal disease proposed by Nenov and colleagues [9]. Lower birthweight [19] and PSGN presumably represent manifestations of early life nephron deficit (under-endowment and childhood loss, respectively), and the significant interaction terms confirm their compounding effects. Higher BMIs potentially potentiate nephron stress through trophic, metabolic and haemodynamic stressors. These are well described in the literature, but often in the context of more marked elevations of BMI [20]. Detection of this effect around the generally modest levels of BMI in the study population probably reflects their operation on a background of pre-existing nephron deficiency. The additional possibility of a genetic predisposition to renal disease is under investigation.

Minimization of the impact of these early life risk factors is critical. Birthweights have been steadily rising since the mid-1960s, with a current mean of about 3.10 kg, compared with 2.79 kg in this study cohort and 2.45 kg in people born from 1956 to 1964 [4, 12, 13, 21]. There is little evidence yet of maternal diabetes complicating this scenario. However, the PSGN situation remains dire, with sporadic cases and epidemics persisting up through the present time. A vaccine against group A streptococcus (GAS) offers some hope [22]. However, elimination of PSGN should not rely on that intervention, but on modification of the global environment of poor hygiene, poor infrastructure, poor nutrition, on-going chronic and acute inflammation and high exposure to pathogens of all sorts.

We have repeatedly emphasized albuminuria’s value as a predictor of non-renal as well as renal events. It predicts development of diabetes and ischaemic heart disease and predicts non-renal natural death of cardiovascular and other causes [6–8]. Therefore, the amplifying effect of early life risk factors probably applies to these conditions as well. We have already shown that young adult natural deaths in this population are preferentially segregated among those with lower birthweights.
Further follow-up of this particular cohort should ultimately disclose non-renal outcomes in the context of both early life risk factors.

The higher level of albuminuria in females applies to Australian Aboriginal people in remote regions across Australia and is ultimately reflected in higher rates of renal failure for females in these settings [23]. Lower birthweights, equal or higher rates of PSGN, higher BMIs and higher rates of diabetes partly explain this phenomenon, and the constitutionally lower nephron numbers in females than males, as demonstrated in several ethnic groups globally [24, 25], probably have a role.

Strengths of this study cohort include the uniform availability of birthweights and of fairly reliable records of recognized episodes of PSGN. Limitations include the relatively small absolute numbers of participants, defined by the size of the community, so that numbers in various birthweight and PSGN subcategories are restricted. ‘Birthweight’ is a clumsy surrogate for appropriate intrauterine growth, and categorical definitions of LBW are of limited sensitivity. In addition, there was likely under-ascertainment of PSGN, which was variably based on obvious clinical presentations between epidemics, and proactive screening during epidemics. Finally, the relative deficiency of young women in the cohort, related to absences for pregnancy, family commitments and menstruation at the time of screening, is a limitation.

This is the only longitudinal study of this kind and detail of any Aboriginal community. Findings are probably relevant to populations in similar circumstances. They give hope for eventual containment of the epidemic of renal and cardiovascular disease in such populations through continued focus on maternal and child health and prevention and containment of infections.

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CONFLICT OF INTEREST

The authors report no conflict of interest regarding this manuscript. The authors confirm that the results presented in this paper have not been published previously in whole or part, except in abstract format.

REFERENCES

22. Group A streptococcal vaccine development: current status and issues of relevance to less developed countries, WHO/FCH/CAH/05.09, WHO/IVB/05.14

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