

Post-streptococcal glomerulonephritis is a strong risk factor for chronic kidney disease in later life.

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Abstract

Our aim was to evaluate, in a remote Aboriginal community with high rates of renal and cardiovascular disease, whether episodes of acute post-streptococcal glomerulonephritis (PSGN) increase risk for chronic kidney disease in later life. Subjects were community members who participated in a health screen from 2004-2006. Albumin/creatinine ratios (ACRs) were measured on random urine samples and medical records were reviewed for histories of episodes of acute PSGN. 1519 people participated in the screen, or about >85% of those age-eligible. High levels of albuminuria and increases with age were confirmed. 200 people had had episodes of PSGN, 27 people on more than one occasion, usually in childhood. All episodes were associated with group A streptococcal skin infections, often associated with scabies. Of people ages 10 to 39 yr at screening, 18.4% of males and 21.6% of females had such a history. Among them, a history of "remote" PSGN (≥ 5 years earlier) was associated with higher levels of ACR than in those without, $p < 0.0001$ for females and $p < 0.0001$ for males. Furthermore, in females age 30-39 years, a PSGN history was associated with a higher frequency of estimated glomerular filtration rate < 60 ml/min (14% vs 0%, $p = 0.0003$). The adjusted odds ratios (CI) for ACR ≥ 34 gm/mol (300 mg/gm, or overt albuminuria) in males and females with a remote history of PSGN, when compared with those without such a history, were 4.6 (1.9-11.1) and 3.1 (1.5-6.3) respectively. We conclude that PSGN is contributing to the very serious burden of CKD in this community. Rigorous strategies to prevent scabies and Group A streptococcal infections will reduce the burden of kidney disease.

Keywords: Post streptococcal glomerulonephritis, chronic kidney disease, albuminuria, scabies.

Introduction

Although now unusual in western countries and in Australia in general,(1) post-streptococcal glomerulonephritis (PSGN) is still common in Australia Aboriginal children living in remote communities, (2-5) where scabies is common and group A streptococcal pyoderma is endemic. PSGN occurs in both sporadic and epidemic forms. In these communities, chronic renal disease and end-stage renal failure also occur in adults at alarming rates.(6,7)

PSGN is usually followed by clinical recovery over several days to weeks, and the long-term outlook has generally been regarded as excellent, with no increase in risk of urinary abnormalities or hypertension.(8-10) However, some studies have suggested that there is an increase in chronic renal impairment after this illness.(11,12)

In one high risk Aboriginal community we described persisting urine abnormalities among 62 children who had symptomatic PSGN during specific epidemics in the 1980s,(4) and higher rates of microalbuminuria in people with a clinical history of PSGN at ages 15-29 years.(13) We now evaluate in that same community, the association of documented episodes of PSGN with albuminuria during a second community-wide conducted from 2004-2006, or more than 10 years later.

Results.

1519 people participated in the screening program, or about 85% of the age-eligible population. Of these, 200 had a history of PSGN recorded in their clinic charts: 173 had a single episode, and 27 had two or more episodes. Figure 1 shows the timing of those episodes, all of which had been documented since 1970. There were major epidemics in the early 1980s and in 1987, and smaller epidemics in 1994, 1999/2000 and in 2005, as well as substantial numbers of endemic cases throughout. There is limited information on streptococcal serotypes prior to the year 2000, but many cases were emm55 by anecdotal recall. In the year 2000 recorded serotypes in cases included emm49.4, emm95 and emm86, in 2001 one case was emm1105, and in 2005 cases were mostly

emm55 (Catherine Marshall and Bart Currie, Menzies School of Health Research, personal communication). Table 1 shows the numbers and proportions of people by sex and age group who had such a history. **In all, 16.5% (n=92) of males and 19% of females (n=85) aged 5-39 years** had a documented history of PSGN. Rates in people age ≥ 40 years at screening were lower than in younger people, and as noted above, they are excluded from further analyses.

Participants were then restricted to those age 10-39 years at examination, with ACR values available on the community screen. Those without a PSGN history were compared with those with a PSGN history recorded ≥ 5 years prior to the examination. These constituted 969 persons, of whom 177 (18.7%) had a PSGN history, ≥ 5 years earlier - 16.5% of males and 20.7% of females, as shown in Table 2. The table also shows that the PSGN episodes had usually occurred in childhood. The average time since the episodes for those age 20-29 years at screening was about 18 yr, and for those who were 30-39 yr olds at screening it was 25 yr.

Table 3 compares some characteristics of those without and with a remote history of PSGN and those with on history of PSGN. Those with a PSGN history were somewhat older, on average, compatible with the major epidemics in the 1980s. There were no significant differences between the groups in BMI, blood pressure, CRP or lipid levels (apart from a lower LDL level in males with a PSGN history). Those with PSGN tended towards higher rates of diabetes than those without; however, this was not significant with adjustment for age, and HBA1c levels were not different. Among the “renal” indicators, average serum creatinine levels were higher in females with a remote history of PSGN than those without. In addition, people with a PSGN history tended towards higher rates of hematuria, had significantly higher rates of proteinuria by dipstick, had higher mean ACR levels and were more likely to have “elevated” levels of ACR by category than those without a PSGN history. It is noteworthy that most individuals with high ACR levels (≥ 34 mg/mmol) also had proteinuria, ie. 81% of males and 93% of females, with $p < 0.0001$ for the association between the two in both sexes.

Table 4 shows trends towards higher ACRs in those with a remote PSGN history in all age groups and in both sexes. There were no differences in e-GFR according to PSGN history in

any age group in males, and none had e-GFR <60. However, in females age 30-39 years there was a trend towards lower eGFRs in those with a PSGN history, and 12% of that group had “low” GFR levels, which was significantly higher than the 0% in those without such a history ($p=0.0003$).

Figure 2 compares the distribution of ACR according to a remote PSGN history in both males and females. In all groups those with PSGN had a broader distribution of ACR values than those without, and the mean values were notably higher in those with PSGN in the two older age groups. Figure 3 also demonstrates the higher average values of ACR in the PSGN groups. Figure 4 shows that trends to higher categories of ACR in those with PSGN are apparent in both sexes across all age groups.

Table 5 summarizes the risk exacerbations for albuminuria above the microalbuminuria threshold ACR ≥ 3.4 , and above the overt albuminuria threshold (ACR ≥ 34) according to a remote history of PSGN, adjusted for age. A history of PSGN was associated with an almost 3-fold increase in rates of ACR ≥ 3.4 and a >3-fold increase in overt albuminuria in males, and with more than 2-fold increases of each in females. The strength of these associations was unchanged or strengthened with adjustment for BMI, blood pressure and diabetes.

Among people who were 20-39 years old at screening, neither the time since the PSGN episode nor the age at the PSGN episode were significant determinants of renal function at screening.

Discussion

Documented episodes of PSGN, both epidemic and sporadic, have been very common since 1970 in this Aboriginal group. In the mid 2000s, about 15% of adolescents (10-19 yr) and more than 20% of young adults (20-39 yr) had such a history recorded, with females equally or more often affected than males. In both sexes, those with a history of PSGN 5 or more years earlier, in whom acute inflammatory effects of PSGN should have subsided, had higher average levels of ACR than those without such a history, and were 3 to 4 times more likely to have elevated levels of ACR at the microalbuminuria and the overt albuminuria cutoffs. They also tended towards higher rates of

proteinuria, and hematuria by dipstick. In addition, 12% of females age 30-39 yr with a remote PSGN history had low levels of e-GFR by the standard definition.

Thus PSGN contributes to the burden of CKD in this community. In view of the powerful predictive value of baseline levels of albuminuria for CKD progression and for both nonrenal and renal deaths,(14,15) it must also contribute to this community's high rates of renal failure and premature nonrenal mortality.

The findings are consistent with the higher prevalence of microalbuminuria documented more than 10 years earlier in the same community in people age 15-29 years with a recorded PSGN history.(13) They are also compatible with a case-control study showing high levels of albuminuria in children who had had PSGN during the 1980s epidemics.(4) The current study adds value in the embrace of all recorded episodes of GN between 1970 and 2005; in the greater number of people with PSGN examined, specification of a 5+ yr interval to define delayed sequelae of PSGN, and the more advanced age (≥ 10 years greater) of the older participants. In an environment where ACR levels increase with age,(13) the progression into adult life of people who had episodes of PSGN in childhood allows more fulsome expression of its renal damaging effects. It particularly illuminated the association of a remote history of PSGN with higher rates of overt albuminuria, whose role as a marker of kidney disease and predictor of renal and nonrenal death is now incontrovertible.(13-15) The demonstration of lower GFRs in some subjects with a PSGN history, **specifically females age 30-39 yr, is also new.**

Thus our knowledge of long term sequelae of PSGN is expanded.(1,8-12,16-21) Demonstration in other settings of a reduced renal functional reserve supports such an association.(22,23) The data suggest that, in some people, kidney damage persists or is superimposed years after the acute PSGN episodes. Persisting or secondary inflammation, as well as hyperperfusion or hypertrophy of remaining nephrons/glomeruli following loss of a critical number of nephrons could both be among the mechanisms.(24) Kidney biopsy data in this and other remote Aboriginal settings are supportive, showing high rates of post-infectious GN and glomerulomegaly which presumably marks compensatory hypertrophy.(25,26)

Strengths of this study include the excellent ascertainment in the screen, the availability of the clinical records, the sweep of the historical information over 35 years, and the detailed knowledge of the distribution, associations and natural history of renal disease in this community.(13-15) The striking frequency of PSGN, and the high density of other nephropathic factors in this environment have probably helped reduce the phenomenon. Weaknesses include the variable sensitivity to PSGN episodes over time, and failure to detect some cases of PSGN have probably resulted in underascertainment of its contribution to CKD. In hindsight, health workers comment that, in non-epidemic years and in the lead up to recognized epidemics, a child appearing “puffy” has sometimes not been further evaluated. In these settings, too, asymptomatic cases are entirely missed, although heightened consciousness and some targeted screening precipitated by symptomatic cases heralding epidemics result in more case-finding at those times. Undiagnosed cases probably contribute to some of the “unexplained” albuminuria in community members without a recognized PSGN history. However, asymptomatic episodes are likely to be associated with a less serious acute course, as well as less marked long term consequences through lower levels of permanent nephron loss.

The data support the inclusion of PSGN as one vital factor in the multideterminant model of albuminuria. Such a model was first formulated in this community,(13) and is conceptually supported by the “multihit” hypothesis of renal disease later proposed by Nenoff and colleagues.(27) Other factors whose significant association with albuminuria we have modeled include age, lower birthweights, skin sores and scabies, non-skin infections (specifically with *H. pylori*), high CRP levels, levels of glycemia, lipids, current body weight and central fat deposition.(13,28) The presence of a persistent specific antistreptococcal antibody, evaluated in a limited number of screened subjects, was also associated with higher levels of proteinuria, with the effect amplified by concurrent overweight or obesity.(29) Lower birthweights, skin sores, scabies and PSGN are among early life determinants. Presumably presence or establishment of an early nephron deficit sets the stage for further cascading nephron loss based on hyperperfusion/ hyperfiltration.(24) The notable female predominance in renal disease and renal failure in this and other remote Aboriginal settings(7,13) might be partly explained by the equal susceptibility of girls and boys to PSGN, the documented lower

birthweights in females,(30) their greater accrual of body fat as adults, and the lower nephron endowment in females generally as demonstrated through autopsy studies.(31,32)

PSGN has been called a disease of transition. Previously these Aboriginal people lived in small groups, were nomadic and did not have permanent dwellings. Now they live in very crowded, poorly ventilated, poorly maintained, dirty houses, where scabies thrives and Group A streptococci spread easily. We cannot comment on the occurrence of PSGN prior to the observation period, but a community death register and, more recently, dialysis registries, suggest that renal failure has increased dramatically since the late 1970s. This, we propose, is fuelled in part by PSGN and infections related to crowding, poor hygiene and poor nutrition, while phenomena associated with lifestyle and health transition, and improved survival of low birthweight infants have also contributed.(30) Against this background of precipitating factors, the possibility of a genetic contribution to disease susceptibility is also being explored.

The frequency of PSGN in this era in a western country is astonishing. The elimination of scabies, the marker of the environment in which PSGN and other third world diseases flourish, must be a top priority in this and other remote communities. This is a matter of wholesale improvement across all sectors such as housing, nutrition and education. Justification could be provided based on cost savings in renal replacement therapy alone. The imminent trialling of anti-streptococcal vaccine could be extended to renal outcomes, rather than the exclusive rheumatic heart disease endpoints for which it was developed.(33) Nonetheless, the virtual elimination of PSGN in westernized environments was achieved without such a vaccine, and no less should be expected for Aboriginal people.

Methods

A community-wide health screen was performed from 2004-2006 in a remote Australian Aboriginal community with high rates of renal and cardiovascular disease, on all volunteers age 5+ years. Assessments **included** urinary albumin concentrations and albumin/creatinine ratios (ACRs) on random urine samples. Medical records were reviewed for notation of episodes of acute PSGN in

their past. Associations of albuminuria with histories of PSGN at least 5 years prior to screening were evaluated in people less than age 40 yr at screening.

The first diagnosis of PSGN was extracted from review of the local clinic records. A diagnosis was based on a compatible clinical picture, defined by urine abnormalities (essential), accompanied by edema and/or hypertension and/or compatible serologic changes, including elevated levels of antistreptococcal antibodies and low levels of total hemolytic complement and/or C3.(4) The date of diagnosis had also been noted in all but 5 cases.

The earliest documentation of episodes of PSGN in clinic records of participants in the screen was in 1970, within a few years of the arrival of the first pediatrician in the Northern Territory, Dr Alan Walker. We do not know if few episodes occurred earlier, or were not recognised or not recorded. To minimize failure of case ascertainment in early life we therefore restricted the analysis to people who were less than <40 years of age at time of screening. That age cut off also minimises bias created by premature mortality in this community, where the median age of adult death is about 47 years, and where, as we have shown, albuminuria predicts all the causal renal death and much of the non-renal natural death.(14) Evaluation of the association of episodes of PSGN with chronic renal disease were confined to subjects whose most recent episode of PSGN had been at least 5 years prior to screening, to minimize lingering contributions of still-recovering acute PSGN episodes to potential urine or renal functional abnormalities. This requirement necessarily excluded the five people with PSGN without a recorded date of diagnosis, and most of the children with a PSGN history who were age 5-9 years old at screening; thus the youngest age group was likewise not included in subsequent analyses.

Descriptive statistics are presented as means, standard deviations and ranges, or as geometric means and 95% confidence intervals for continuous variables as appropriate, or as percentages and 95% confidence intervals for categorical variables. Comparisons by PSGN status were made using t-tests or Wilcoxon rank sums tests for continuous variables and by chi-squared test or Fisher exact test for categorical variables as appropriate. Logistic regression was used to determine the association between a history of remote PSGN and specific

renal parameters with separate models developed for each sex. All statistical tests were two tailed and the threshold of statistical significance was $p < 0.05$. Analyses were performed using Stata version 11.1 statistical software.(34)

Disclosure

All the authors declare no competing interests.

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Titles and legends:

Table 1. Distribution of people with a history of PSGN, by age and sex

Table 2. Descriptive statistics for people with a remote history of PSGN (≥ 5 yr prior)

Table 3. Characteristics of subjects by a remote history of PSGN (≥ 5 years prior) by sex.

Mean (SD) except where otherwise specified. All p values reported are adjusted for age.

Table 4 Renal parameters by a remote history of PSGN (≥ 5 years prior) by sex and age group (number of participants in *italics*).

Table 5. Odds Ratios (95%CI) for renal parameters by history of remote PSGN (≥ 5 years prior) in people age 10-39 years at screening. Referrent group: people without a history of PSGN.

Figure 1. Episodes of PSGN since 1970 by year of occurrence.

Figure 2. ACR levels by sex and age group according to a remote history of PSGN (≥ 5 years prior)

Figure 3. ACR levels by sex and age group according to a remote history of PSGN (≥ 5 year prior)

Figure 4. ACR categories by sex and age group according to a remote history of PSGN (≥ 5 years prior)

Tables

Table 1.

Age group	Males	Females
5-9 yr	9/70 (12.9%)	4/79 (5.1%)
10-19 yr	23/170 (13.5%)	21/141 (14.9%)
20-29 yr	35/220 (15.9%)	37/139 (26.2%)
30-39 yr	38/176 (21.6%)	34/145 (23.4%)
40+ yr	9/174 (5.2%)	5/205 (2.4%)

Table 2.

Males			
Age group	PSGN: n	Age at PSGN (yrs): Mean (SD), range	Time since PSGN (yrs): Mean(SD), range
10-19 yr	20	5.1 (2.9), 0.9-10.5	11.7 (4.2), 5.3-18.7
20-29 yr	35	6.7 (3.8), 2.2-22.3	17.9 (4.0), 7.3-24.8
30-39 yr	37	10.0 (4.1), 0.3-22.3	24.2 (3.1), 11.7-35.0
Females			
Age group	PSGN: n	Age at PSGN (yrs): Mean (SD), range	Time since PSGN (yrs): Mean (SD), range
10-19 yr	16	4.9 (2.8), 1.3-11.3	10.7 (2.9), 5.4-16.6
20-29 yr	36	7.2 (3.8), 0.02-15.4	18.3 (4.4), 10.8-29.0
30-39 yr	33	11.5 (6.7), 5.1-33.8	22.4 (6.2), 5.6-32.2

Table 3.

	Non PSGN N=465	PSGN N=92	P
Males			
Age (yrs)	24.7 (8.6)	27.6 (7.2)	0.02
BMI (kg/m ²)	21.4 (5.0)	21.0 (3.8)	0.14
SBP (mmHg)	116.8 (15.2)	117 (14.0)	0.55
DBP (mmHg)	72.1 (11.7)	72.2 (11.4)	0.28
S Creatinine (μmol/L) ¹	81.4 (19.0)	82.1 (12.3)	0.93
HDL (mmol/L) ²	1.3 (0.3)	1.3 (0.3)	0.12
LDL (mmol/L) ²	2.7 (0.8)	2.4 (0.9)	0.02
Trigs (mmol/L) ²	1.6 (1.2)	1.8 (1.7)	0.11
CRP (mg/L) ²	6.8 (11.3)	5.5 (5.3)	0.30
HbA1c (%) ²	5.7 (0.5)	5.7 (0.5)	0.98
Diabetes ³	3.4 (2.0-5.5)	7.6 (3.1-15.1)	0.24
Proteinuria >1+ ³	20.2 (16.7-24.2)	27.2 (18.4-37.4)	0.31
Hematuria >small ³	7.1 (4.9-9.8)	13.0 (6.9-21.7)	0.04
uACR (mg/mmol) ⁴	1.50 (1.3-1.7)	2.95 (2.1-4.2)	0.002
ACR ³ <3.4	80 (76.1-83.6)	57.6 (46.9-67.9)	0.001
3.4-33	16.5 (13.3-20.2)	30.4 (21.3-40.9)	
34+	3.4 (2.0-5.5)	12 (6.1-20.4)	
Females			
	Non PSGN N=325	PSGN N=85	P
Age (yrs)	24.5 (8.9)	27.2 (6.8)	0.01
BMI (kg/m ²)	22.9 (6.5)	24.3 (6.3)	0.59
SBP (mmHg)	110.9 (13.3)	112.4 (14.1)	0.81
DBP (mmHg)	71 (10.7)	72 (10.3)	0.88
S Creatinine (μmol/L) ¹	56.6 (9.7)	61.2 (24.5)	0.01
HDL (mmol/L) ²	1.3 (0.3)	1.3 (0.4)	0.82
LDL (mmol/L) ²	2.4 (0.7)	2.4 (0.8)	0.74
Trigs (mmol/L) ²	1.6 (1.4)	1.9 (1.6)	0.20
CRP (mg/L) ²	9.2 (9.8)	9.4 (10.2)	0.88
HbA1c (%) ²	6.0 (1.1)	6.1 (1.3)	0.66
Diabetes ³	11.1 (7.9-15.0)	15.3 (8.4-24.7)	0.85
Proteinuria ≥1+ ³	18.0 (14.1-22.8)	32.9 (23.1-44.0)	0.02
Hematuria ≥ small ³	11.5 (8.1-15.3)	18.8 (11.2-28.8)	0.07
uACR (mg/mmol) ⁴	2.8 (2.4-3.3)	6.5 (4.2-10.1)	0.005
ACR ³ <3.4	66.3 (60.8-71.4)	43.5 (32.8-54.7)	0.002
3.4-33	25.2 (20.5-30.2)	34.1 (24.2-45.2)	
34+	8.6 (5.8-12.2)	22.4 (14.0-32.7)	

¹ Males: n = 398 non-PSGN, 87 PSGN; Females: n = 266 non-PSGN, 83 PSGN

² Males: a minimum of 397 non-PSGN and 83 PSGN;
Females: a minimum of 258 non-PSGN and 79 PSGN

³ % (95% CI)

⁴ gmean, (95% CI)

Table 4.

Males:

Age	Urine ACR ¹		eGFR (MDRD) ²		eGFR<60 ³	
	No PSGN	PSGN	No PSGN	PSGN	No PSGN	PSGN
10-19 yr	1.0 (0.9-1.1) 146	1.3 (0.7-2.4) 20	147.0 (46.7) 85	130.1 (21.8) 17	0 (0-4.2)* 85	0 (0-20)* 17
20-29 yr	1.1 (1.0-1.3) 182	2.9 (1.6-5.2) 35	105.5 (16.2) 179	106.0 (19.6) 34	0 (0-2.0)* 179	0 (0-10)* 34
30-39 yr	3.4 (2.6-4.5) 138	4.7 (2.7-8.2) 37	99.4 (19.8) 134	98.3 (15.1) 36	1.5 (0.2-5.3) 134	0 (0-10)* 36

Females:

Age	Urine ACR ¹		eGFR (MDRD) ²		eGFR<60 ³	
	No PSGN	PSGN	No PSGN	PSGN	No PSGN	PSGN
10-19 yr	1.5 (1.3-1.8) 117	2.2 (0.9-5.5) 16	146.8 (30.9) 58	137.3 (24.2) 14	0 (0-6.2)* 58	0 (0-23.2)* 14
20-29 yr	2.3 (1.8-2.9) 99	4.9 (2.5-9.5) 36	125.6 (24.9) 99	125.0 (27.1) 36	0 (0-3.7)* 99	0 (0-10)* 36
30-39 yr	6.4 (4.6-8.8) 110	14.8 (7.2-30) 33	110.8 (21.9) 109	106.8 (33.0) 33	0 (0-3.2)* 109	12.1 (3-28) 33

¹ urine ACR: gm/mol, geometric mean (CI);

² eGFR, arithmetic mean (SD)

³ eGFR < 60, percent (CI),

*one-sided, 97.5% CI

Table 5.

	Renal outcome	
Males	ACR \geq 3.4	ACR \geq 34
Adjusted for age	2.88 (1.7-4.8)	3.52 (1.5-8.0)
Adjusted for age, BMI, SBP, DBP, diabetes	3.22 (1.9-5.6)	4.96 (1.9-12.6)
	Renal outcome	
Females	ACR \geq 3.4	ACR \geq 34
Adjusted for age	2.26 (1.4-3.8)	2.86 (1.5-5.6)
Adjusted for age, BMI, SBP, DBP, diabetes	2.38 (1.4-4.1)	3.33 (1.6-7.0)

Figure 1. Episodes of PSGN since 1970 by year of occurrence.

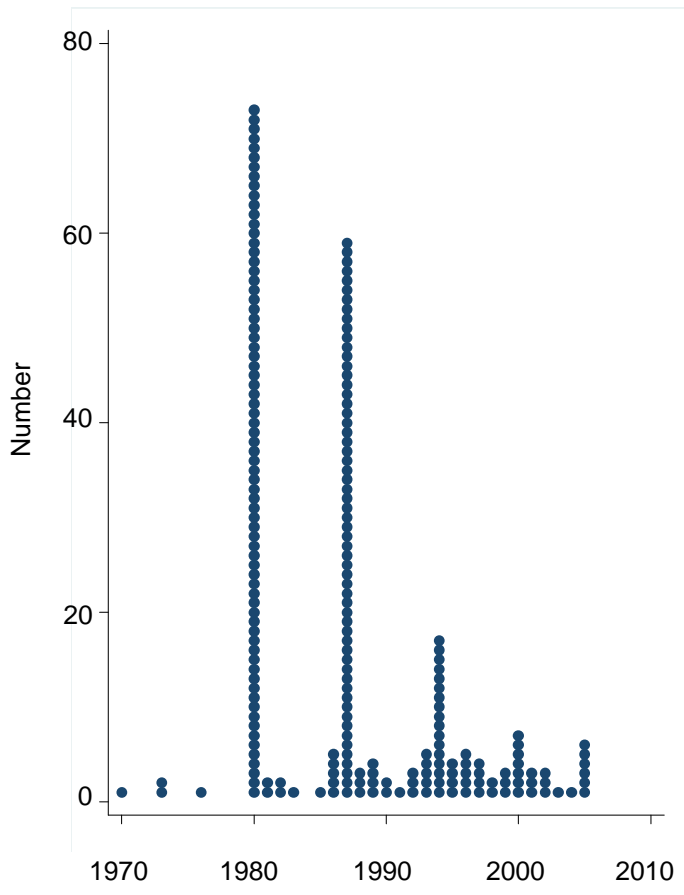


Figure 2. ACR levels by sex and age group according to a remote history of PSGN (≥ 5 years prior)

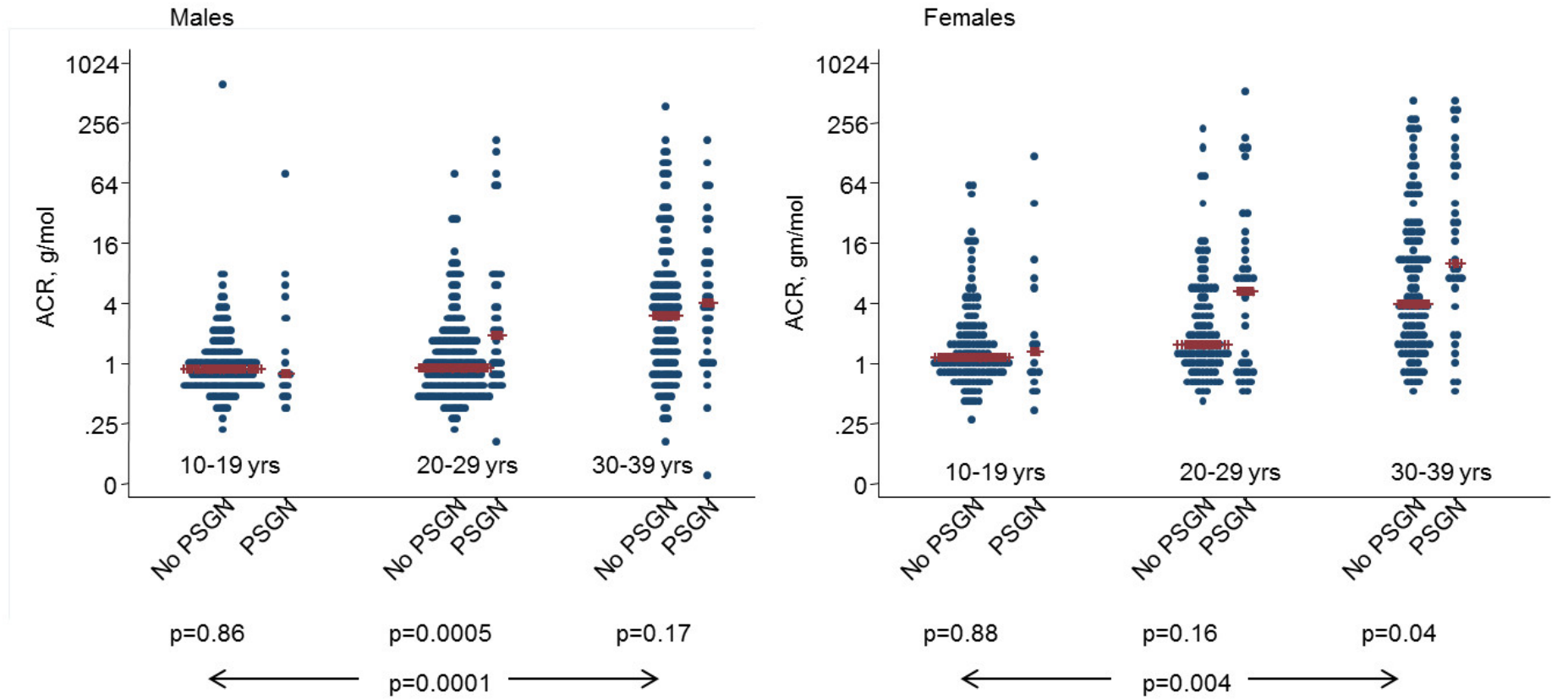


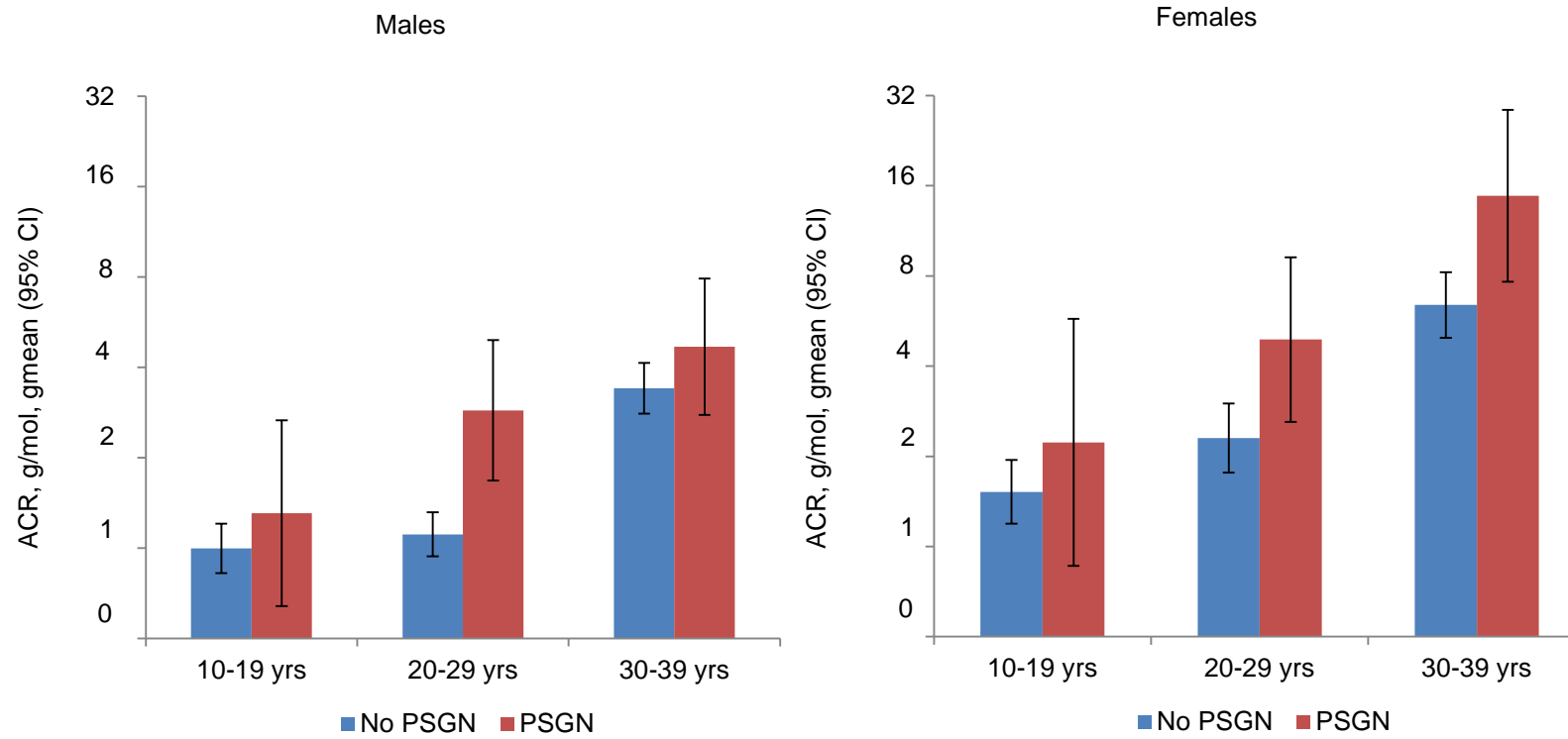
Figure 3. ACR levels by sex and age group according to a remote history of PSGN (≥ 5 year prior)

Figure 4. ACR categories by sex and age group according to a remote history of PSGN (≥ 5 years prior)

