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Complete List of Authors:	Larkins, Nicholas; The Children's Hospital at Westmead, Centre for Kidney Research; University of Sydney, School of Public Health Kim, Siah; The Children's Hospital at Westmead, Centre for Kidney Research; University of Sydney, School of Public Health Carlin, John; Murdoch Children's Research Institute; University of Melbourne, Melbourne School of Population and Global Health Grobler, Anneke; Murdoch Children's Research Institute Burgner, David; Murdoch Children's Research Institute; University of Melbourne, Department of Paediatrics Lange, Katherine; Murdoch Children's Research Institute Craig, Jonathan; University of Sydney, School of Public Health; The Children's Hospital at Westmead, Centre for Kidney Research Wake, Melissa; Murdoch Children's Research Institute; The University of Auckland, Department of Paediatrics & The Liggins Institute
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Albuminuria: Population epidemiology and concordance in 11-12 year old Australians and their parents

Larkins NG,[1-3] Kim S,[1,4] Carlin J,[5,6] Grobler AC,[5] Burgner DP,[5,7,8] Lange K,[5] Craig JC,[1,2] Wake M.[5,9]

Affiliations: [1] Centre for Kidney Research, The Children's Hospital at Westmead, Westmead, NSW, Australia; [2] School of Public Health, University of Sydney, Sydney, NSW, Australia; [3] Department of Nephrology, Princess Margaret Hospital, Subiaco, WA, Australia; [4] School of Women's and Children's Health, University of New South Wales, Sydney, NSW, Australia; [5] Murdoch Children's Research Institute, Royal Children's Hospital, Parkville, VIC, Australia; [6] Melbourne School of Population and Global Health, Faculty of Medicine, Dentistry and Health Services, University of Melbourne, Parkville, VIC, Australia; [7] Department of Paediatrics, The University of Melbourne, Melbourne, VIC, Australia; [8] Department of Paediatrics, Monash University, Melbourne, VIC, Australia; [9] Department of Paediatrics & The Liggins Institute, The University of Auckland, Auckland, New Zealand.

Correspondence to: Professor Melissa Wake
Murdoch Children's Research Institute
The Royal Children's Hospital
50 Flemington Road, Parkville 3052, VIC Australia
T: +61 3 9345 5761
E: melissa.wake@mcri.edu.au

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Abbreviations: ACR: albumin-to-creatinine ratio; AHS: Australian Health Survey; BMI: body mass index; CC: Pearson's correlation coefficient; CheckPoint: Child Health CheckPoint; CI: confidence interval; IQR: interquartile range; Disadvantage Index: Index of Relative Socio-economic Disadvantage; KDIGO: Kidney Disease Improving Global

Outcomes; L: litres; LSAC: Longitudinal Study of Australian Children; mg: milligrams; mmol: millimoles; n: number in category; N: number with valid data for characteristic; NHANES: National Health and Nutrition Examination Survey; RC: estimated regression coefficient; SD: standard deviation.

ABSTRACT

Objectives: To describe the distribution of albuminuria among 11 to 12-year old Australian children and their parents, and assess its intergenerational concordance within parent-child dyads.

Design: Population-based cross-sectional study (the Child Health CheckPoint), nested within the Longitudinal Study of Australian Children.

Setting: Assessment centres (six capital cities and eight regional cities) and home visits across Australia, February 2015 to March 2016.

Participants: Of all participating CheckPoint families (n=1874), 1557 children (46.2% girls) and 1454 parents (85.5% mothers) provided random urine samples at the visit; samples from menstruating females were excluded.

Outcome measures: Urine albumin-to-creatinine ratio (ACR) and its components (urine albumin and creatinine concentration); albuminuria was defined as an ACR ≥3.4 mg/mmol. Pearson's correlation coefficients and multivariable linear regression models assessed parent-child concordance, using log-transformed data due to skewing. Survey weights and methods were applied to account for the complex sample design.

Results: The median ACR for children was 1.03 mg/mmol (interquartile range (IQR) 0.65 to 1.97) and 1.01 mg/mmol (IQR 0.60 to 2.09) for adults. The median ACR was higher in girls (1.20, IQR 0.71 to 2.65) than boys (0.90, IQR 0.61 to 1.65) and in mothers (1.13, IQR 0.63 to 2.33) than fathers (0.66, IQR 0.41 to 1.05). Albuminuria was detected in 15.1% of children (girls 20.8%, boys 10.1%) and 13.5% of adults (15.1% mothers, 4.0% fathers) had albuminuria. There was a small correlation between parent and child ACR (Pearson correlation coefficient 0.06, 95% confidence interval 0.01 to 0.12).

Conclusions: Albuminuria is common among Australian children and adults, which is of concern because it predicts risk for kidney and cardiovascular disease, and mortality. The weak concordance among inter-generational pairs for urine ACR suggests either that genetic hereditability is low or that it becomes evident only at later offspring life stages.

Strengths and limitations of this study

- Australia-wide population-based cohort sampled using a multi-stage, clustered survey design allowing for the derivation of accurate population-level estimates.
- Large sample of biological parent-child pairs allowing for precise estimates of intergenerational concordance.
- First morning or timed urine samples were not available to investigate the impact of orthostatic variation on urine ACR. The estimates of prevalence would be lower if participants with intermittent proteinuria were identified and excluded.
- The single (rather than repeated) urine ACR value makes the study open to residual measurement error.

INTRODUCTION

Albuminuria, even at low levels, is an important marker of chronic kidney disease and strongly predicts end-stage kidney disease.[1, 2] It also independently predicts cardiovascular events and all-cause mortality, probably as a reflection of endothelial dysfunction.[3] There are different methods of measuring albuminuria. The reference standard, 24-hour urine collection, is impractical in many settings, so that spot urine albumin-to-creatinine ratio (ACR) is routinely used in clinical practice. Urine ACR and spot urine albumin concentration reliably estimate 24-hour albumin excretion, although the correlation is stronger for ACR because it accounts for differences in urine concentration due to hydration status.[4] There are also postural changes in albumin excretion.[5] However, because the timing of collection tends not to correlate with explanatory variables of interest (eg socio-economic status or age) this does not introduce confounding. Consequently, random samples are routinely used for research purposes also and most evidence relating albuminuria to kidney and cardiovascular risk derives from random urine ACR.[6]

Despite the potential utility of urine ACR as a cheap, non-invasive biomarker, data about the normal distribution of ACR and its components in children are mostly limited to disease-specific contexts.[7] In children with type 1 diabetes mellitus, persistent or intermittent microalbuminuria predicts the future development of macroalbuminuria, and in children with renal dysplasia or glomerular pathology albuminuria is also predictive of long-term renal function.[8-12] However, the population-based data that are available in children suggest some important discrepancies compared to adults. For example, whereas obese adult have higher rates of albuminuria, the reverse has been reported in children (an odds ratio of 0.34 for albuminuria in overweight and obese compared to normal weight children).[13] In addition, orthostatic proteinuria, generally considered to be a benign condition, may affect up to 20% of children 9 to 16 years old.[13-15]

Among adults, given the clear relationship between albuminuria and future cardiovascular events or chronic kidney disease, there has been a shift in focus from pathological levels to the risk associated with urine ACR levels in the low-normal range. The Chronic Kidney Disease Prognosis Consortium has shown through collaborative meta-analysis that a urine ACR of 1.1 mg/mmol is associated with a hazard ratio of 1.20 for all-cause mortality (95% confidence interval [CI] 1.15 to 1.26) compared to a urine ACR of 0.6 mg/mmol.[6] Such relationships, where risk extends below traditional thresholds into the normal range, are

common among clinical biomarkers and make it difficult to define the threshold at which values should be considered abnormal.[16 17]

It is increasingly recognised that the development of chronic diseases, such as kidney and cardiovascular disease, begins in early life.[18] Through the study of parent-child concordance for early disease markers or risk factors, we can begin to understand the role of inherited genetic and environmental influences in establishing adverse lifecourse trajectories. A sub-study of the Framingham Heath Study involving 1055 adult participants found up to 20% of the population variance in urine ACR may be due to genetic hereditability.[19] Single nucleotide polymorphism data also suggests a genetic component to albuminuria.[20] If concordance is confirmed while offspring are still children, this could provide useful prognostic information early in life as we attempt to develop strategies allowing the earlier identification of people progressing towards disease states, with the ultimate goal of providing earlier interventions to keep people healthy.

The Child Health CheckPoint study nested within *Growing Up in Australia* (also known as the Longitudinal Study of Australian Children, LSAC) provides an important opportunity to examine these issues. We aimed to assess the cross-sectional distribution of urine ACR and related metrics in Australian children aged 11-12 years and their parents, and describe the extent of intergenerational concordance for this measure.

METHODS

Study design and participants: Details of the initial LSAC study design and recruitment are outlined elsewhere.[21] In brief, LSAC recruited a nationally representative sample of 5107 infants[22] using a two-stage clustered design, and followed them up in biennial 'waves' of data collection up to 2015. The initial proportion recruited to the relevant B cohort in 2004 was 57.2%, of whom 73.7% (n=3764) were retained to LSAC wave 6 in 2014.

At the wave 6 visit, all remaining families (n=3513) were invited to consent to their contact details being shared with the Child Health CheckPoint (CheckPoint) team. In 2015, families that consented were then sent an information pack via post and received an information and recruitment phone call. The CheckPoint's detailed cross-sectional biophysical assessment, nested between LSAC waves 6 and 7 (aged 11-12 years), took place between February 2015 and March 2016. 1874 families participated. A more detailed description of the CheckPoint study design is provided in this issue of BMJ Open.[23]

Ethics and Consent: The CheckPoint study protocol was approved by The Royal Children's Hospital Melbourne Human Research Ethics Committee (33225D) and Australian Institute of Family Studies Ethics Committee (14-26). The attending parent provided written informed consent for themself and their child to participate in the study.

Procedure: Urine was collected at a specialised 3.5 hour (capital and large cities) or 2.5 hour (smaller regional centres) CheckPoint assessment centre visits; those families (n=378) who could not attend were offered a shorter home visit (figure 1). Child Health CheckPoint assessments took place between Feb 2015 and March 2016. As assessment centre visits ran throughout the day, sample collection time could be anywhere between 9 am and 6 pm, even though urine collection was requested as part of the first assessment station after check-in. Participants were asked to urinate directly into a polypropylene sterile pot until full (or as best possible), and included in current analyses if they provided a usable sample (figure 1). Results from mothers and girls who self-reported they were menstruating were excluded. Only biological parent-child pairs were included for concordance analysis.

Outcome measure: Urine samples were stored at 4^{o}C until processing (77% of samples processed within three hours and 85% within 13 hours; maximum seven days for home visit participants). They were then pipetted under laboratory conditions into a maximum of 12 x 0.7 mL aliquots and frozen and stored at -80^{o}C. Analysis was performed at the Laboratory of the Baker Heart and Diabetes Institute. Samples were first defrosted over 30 minutes and then centrifuged at 500 rpm for three minutes. A Cobas Integra ® 400 plus analyzer performed the measurements, determining albumin using an immunoturbimetric assay and creatinine using the enzymatic colorimetric method. The lower limit for the detection of urine albumin on this machine is 3 mg/L.

For descriptive purposes ACR was categorised according to the Kidney Disease Improving Global Outcomes (KDIGO) 2012 guidelines: microalbuminuria 3.4 to 34 mg/mmol and macroalbuminuria >34 mg/mmol.[24] We also determined the prevalence of albuminuria among adults using the current Australian guidelines: microalbuminuria in fathers 2.5 to 25 mg/mmol and macroalbuminuria in fathers >25 mg/mmol, microalbuminuria in mothers 3.5 to 35 mg/mmol and macroalbuminuria in mothers >35 mg/mmol.[25] For purposes of this paper, we used the overarching term 'albuminuria' to refer to the combined participants with micro- or macroalbuminuria.

Potential confounders:

Disadvantage score: Our proxy for socio-economic status was the census-based Index of Relative Socio-economic Disadvantage (Disadvantage Index) from the Socio-Economic Indexes for Areas as published by the Australia Bureau of Statistics.[26] This composite, postcode-based measure includes education, income, employment and disability based factors.

Anthropometry: Height was measured twice, three times where the first two measures differed by >0.5 cm, without shoes or socks using a portable rigid stadiometer, and all measurements averaged to produce the final value. An electronic, calibrated scale (lnBody230 scales, Biospace Co. Ltd., South Korea) was used to measure body weight with participants wearing light clothing and no shoes or socks. Body mass index (BMI) for children was converted to z-scores according to the 2000 Centre for Disease Control and Prevention growth charts.[27] Overweight was defined as BMI ≥85th centile and <95th centile, and obesity as BMI ≥95th centile.[28] A steel tape measure was used to measure waist circumference using the cross-hand technique at the narrowest point (or mid-point if no narrowing) between then 10th rib and the top of the iliac crest. Two measurements were taken provided these were within 0.1 cm, otherwise a third measurement was performed. The final value was the mean of the two closest measurements.

Blood pressure: Blood pressure was measured at the brachial artery using an oscillometric device (SphygmoCor XCEL, AtCor Meidcal Pty. Ltd., Australia), following at least 7 minutes of rest, in the supine position. Three measurements were taken with at least one minute of rest between readings. The final value was the average of all three measurements. Hypertension and high-normal blood pressure were defined as a height, sex and age adjusted blood pressure centile ≥95th centile or <95th but ≥90th centile respectively, using the Fourth Report from the National High Blood Pressure Education Program reference thresholds.[29, 30]

Other: Medical history was by obtained by self- or guardian-report. Pubertal status was determined using self-reported responses on the Pubertal Development Scale.[31]

Statistical Analysis: Concordance between parents and children was assessed by: 1) Pearson's correlation coefficients with 95% confidence intervals; and 2) linear regression with child variable as dependent variable and parent variable as independent variable. Linear regression models were adjusted for parent age, Disadvantage Index, and parent and child BMI and sex in models including both sexes. In addition, the Pearson's correlation coefficient and linear regression analyses were repeated using weighted multi-level survey

analyses. These results were similar to the simple correlations and regression results adjusted for stratification and clustering by postcode only, and only the simple results are reported. Two children and one adult showed an ACR >200 mg/mmol or urine albumin concentration > 2000 mg/L. These were included in the distribution statistics consistent with the population-based sampling and aims. However, they were excluded from the concordance analyses because they were outliers and influential observations, considered to represent discrete glomerular pathology.

Population summary statistics and proportions were estimated by applying survey weights and survey procedures that corrected for sampling and participation biases and took into account clustering in the sampling frame. Standard errors were calculated taking into account the complex design and weights.[32] More detail on the calculation of weights is provided elsewhere.[33]

The differences between adult and child, and between male and female, groups were tested for statistical significance using linear or logistic regression. All urine variables were log-transformed for the purposes of hypothesis testing and concordance analysis, due to severe right skewing.

RESULTS

Sample characteristics: Of the 1874 families assessed, 1557 children (83.1%) and 1454 adults (90.0%) contributed valid urine samples for analysis (1301 biological parent-child pairs; figure 1). 22 children and 217 adults were excluded because they were menstruating, and 15 carer-child pairs were excluded from concordance analysis because the adult was a non-biological parent. There were slightly more boys (n=837, 53.8%) than girls (n=720) and most parents were mothers (n=1243, 85.5%) (table 1).

Table 1. Participant characteristics; all values are n (%) except age

Characteristic	Boys			Girls			Fathers†			Mothers†		
	n	N	%*	n	N	%*	n	N	%*	n	N	%*
Age (years), mean* (SD)	835	12.0	0.38	720	12.0	0.4	211	46.7	6.89	1243	43.5	5.35
BMI category												
Overweight	127	836	16.3	107	720	16.8	90	210	42.9	382	1237	31.2
Obese	84	836	12.7	59	720	9.6	71	210	37.2	382	1237	32.4
Blood pressure category												
High-normal	18	787	2.5	26	692	4.1	111	197	57.0	372	1164	32.7
Hypertensive	24	787	4.9	22	692	3.6	31	197	18.1	88	1164	7.8
Socio-economic status quintile												
1st (most disadvantaged)	70	833	13.4	54	719	10.6	17	208	11.9	93	1242	12.2
2nd	128	833	19.6	107	719	17.9	37	208	22.6	181	1242	17.6
3rd	145	833	19.8	134	719	20.6	40	208	23.3	225	1242	20.3
4th	194	833	21.8	179	719	25.1	37	208	15.8	317	1242	24.8
5th (least disadvantaged)	296	833	25.5	245	719	25.8	77	208	26.4	426	1242	25.1
Diabetes	2	837	0.2	3	720	0.6	9	211	4.8	26	1243	2.6
Heart condition	-	-	-	-	-	-	9	211	5.4	24	1243	2.7
Started puberty	686	793	87.8	629	663	94.8	-	-	-	-	-	-

SD: standard deviation; BMI: body mass index; n: number in category; N: number with valid data for characteristic (denominator).
* weighted mean/percentage; † 98.9% of adult participants were biologic parents of participating children.

The participant characteristics were broadly reflective of the Australian population, as per the study design, with the exception that the sample was relatively less disadvantaged than the general population (25.6% of children in the least but only 12.1% in the most disadvantaged national quintile). Consistent with this, most adults and over one quarter of children were overweight or obese (65.9% adults, 27.8% children). There were no major differences in participant characteristics by sex for the childhood cohort. However, mothers were on average younger than fathers (43.5 years vs 46.7 years), fewer had a high-normal BP or hypertension (40.5% vs 75.1%), and fewer were overweight or obese (63.6% vs 80.1%).

Distribution of ACR and albuminuria (table 2 and figure 2):

Children: The median ACR among children was 1.03 mg/mmol (IQR 0.65 to 1.97) (table 2).

Table 2. Distribution of urine albumin, creatinine, albumin to creatinine ratio and albuminuria by age cohort and sex

Variable	Males		Females		All	
	N	Median (IQR)	N	Median (IQR)	N	Median (IQR)
Children						
Albumin (mg/L)	837	5.6 (5.3 to 7.6)	720	6.7 (5.4 to 13.2)	1557	5.9 (5.3 to 9.8)
Creatinine (mmol/L)	837	8.0 (5.0 to 11.3)	720	7.7 (4.5 to 11.3)	1557	7.9 (4.7 to 11.3)
Albumin creatinine ratio	837	0.9 (0.6 to 1.7)	720	1.2 (0.7 to 2.7)	1557	1.0 (0.7 to 2.0)
Adults						
Albumin (mg/L)	211	5.5 (5.2 to 6.6)	1243	5.4 (5.2 to 6.4)	1454	5.4 (5.2 to 6.4)
Creatinine (mmol/L)	211	9.7 (6.0 to 14.8)	1243	5.9 (2.7 to 10.3)	1454	6.4 (3.0 to 11.2)
Albumin creatinine ratio	211	0.7 (0.4 to 1.1)	1243	1.1 (0.6 to 2.3)	1454	1.0 (0.6 to 2.1)
	n/N	**%**[‡]	**n/N**	**%**[‡]	**n/N**	**%**
Children						
Albuminuria*	92/837	10.1	141/720	20.8	233/1557	15.1
Microalbuminuria	85/837	9.5	135/720	20.0	220/1557	14.2
Macroalbuminuria	7/837	0.9	6/720	0.9	13/1557	0.9
Adults						
Albuminuria	9/211	4.0	188/1243	15.1	197/1454	13.5
Microalbuminuria	7/211	2.9	187/1243	15.0	194/1454	13.3
Macroalbuminuria	2/211	1.1	1/1243	<0.1	3/1454	0.2
Albuminuria (sex-corrected)[†]	15/211	6.9	179/1243	14.3	194/1454	13.3
Microalbuminuria (sex-corrected)	13/211	5.8	178/1243	14.3	191/1454	13.1
Macroalbuminuria (sex-corrected)	2/211	1.1	1/1243	<0.1	3/1454	0.2

IQR: interquartile range; n: number in category; N: number with valid data for characteristic (denominator); mg: milligrams; mmol: millimoles; L: litres.
* combined total of micro- and macroalbuminuria; [†] using current Australian thresholds to define albuminuria, 2.5 mg/mmol for fathers and 3.5 mg/mmol for mothers; [‡] weighted percentage.

The median urine albumin concentration for boys was 5.6 mg/L (IQR 5.3 to 7.6) and for girls was 6.7 mg/L (IQR 5.4 to 13.2; p<0.001). Albuminuria was present in 15.1% of children, and albuminuria was more common in girls than boys (20.8% versus 10.1%; p<0.001), largely due to differences in urine albumin as opposed to urine creatinine concentration (figure 2). Percentile values for urine albumin, creatine and albumin-to-creatinine ratio distributions are presented in supplementary tables S1a and S1b.

Adults: The median ACR among adults was 1.01 mg/mmol (IQR 0.60 to 2.09). The prevalence of albuminuria was much higher in mothers than fathers, at 15.1% vs 4.0% respectively (p<0.001) for the KDIGO thresholds, and 14.3% vs 6.9% respectively (p=0.02) for the sex-stratified Australia thresholds, noting that the number of fathers on which this estimate was based was small. Among adults, the sex discrepancy in ACR was driven more by differences in the distribution of urine creatinine than urine albumin concentration (figure 2).

Intergenerational concordance of ACR: A weak positive correlation was present between biological parent and child urine ACR (r 0.06, 95% CI 0.01 to 0.12) and albumin (r 0.06, 95% CI 0.01 to 0.12), with stronger correlations for creatinine values (r 0.19, 95% CI 0.13 to 0.24) (figure 3). These values were essentially unchanged when using partial correlation coefficients to adjust for parent age, socio-economic status, and child and parent BMI and sex (table 3, sex-specific values shown in supplementary tables S2a and S2b). Multivariable linear regression showed some evidence of parent-child concordance for all three urine variables (table 3).

Table 3. Parent-child concordance

Variable			
Pearson's Correlation	**N**	**CC**	**95% CI**
Albumin (mg/L)	1300	0.06	0.01 to 0.11
Creatinine (mmol/L)	1301	0.19	0.13 to 0.24
Albumin creatinine ratio	1300	0.06	0.01 to 0.12
Multivariable Linear Regression*	**N**	**RC**	**P-value**
Albumin (mg/L)	1292	0.09	0.06
Creatinine (mmol/L)	1293	0.15	<0.001
Albumin creatinine ratio	1292	0.07	0.02
Partial correlation coefficient*	**N**	**RC**	
Albumin (mg/L)	1292	0.05	
Creatinine (mmol/L)	1293	0.18	
Albumin creatinine ratio	1292	0.07	

CC: Pearson's correlation coefficient; CI: confidence interval; mg: milligrams; mmol: millimoles; L: litres; RC: estimated regression coefficient.
* Adjusted for parent age, Index of Relative Socioeconomic Disadvantage, child and parent body mass index, parent and child sex. Albumin, creatinine and albumin creatinine ratio have been log transformed.

There was also a weak association between parent-child pairs for albuminuria (ACR ≥3.4 mg/mmol): in 73.3% of pairs neither parent or child had albuminuria, in 11.8% of pairs only the adult had albuminuria, in 12.8% of pairs only the child had albuminuria and in 2.0% both parent and child had albuminuria.

DISCUSSION

Principal findings: In this population-based Australian study, 13.5% of adults and 15.1% of children had albuminuria. The prevalence varied by sex, with albuminuria more common in females among both children and, especially, adults. In children the sex difference was mostly driven by an increased urine albumin concentration, whereas in adults the urine creatinine concentration was relatively more important. There was weak intergenerational concordance for urine albumin and ACR, but creatinine concordance was larger (0.15-0.19).

Strengths and limitations: Strengths of the Child Health CheckPoint study include the large sample size and the multi-stage, clustered survey methodology that together allow for the derivation of accurate population estimates. All samples were processed in a central research laboratory under strict protocols. The main weakness of the data presented here is that first morning or timed samples were not collected, and so we cannot account for the impact of orthostatic proteinuria. We also lacked the ability to account for day-to-day variability in urine ACR, which will result in residual measurement error.[41] Orthostatic proteinuria is a greater issue for children than adults and may have increased the prevalence estimates.[37] There was an over-representation of mothers in the adult cohort, reducing the precision around estimates for fathers. The lack of longitudinal data limits our ability to draw conclusions about the prevalence of albuminuria over time or investigate how this relates to future events.

Findings in relation to other studies: The prevalence of albuminuria among children was similar to other population-based studies. We recently performed an analysis of data from the 2011/13 Australian Health Survey (AHS) and found 12.8% of children aged 5 to 18 years had albuminuria using the same threshold of 3.4 mg/mmol.[13] In the United States, the prevalence of albuminuria in the National Health and Nutrition Examination Survey (NHANES) has been reported as 8.9%.[14] However, in that study the mean age was 15.5 years, and older adolescents appear to have a lower prevalence of albuminuria.[13, 34] In both the AHS and NHANES studies girls had a higher ACR than boys because of differences in urine albumin, rather than differences in urine creatinine concentration. We believe the most likely

explanation for this is that normal physiologic values vary by sex, rather than sex-related differences in cardiovascular or kidney health at this age.

The prevalence of albuminuria and mean values for urine ACR, urine albumin and urine creatinine concentrations were similar in children and adults. This was unexpected because, as a marker of early disease and risk for future clinical cardiovascular and kidney events, we would expect an increase in the prevalence of albuminuria between childhood and mid-adulthood, as is observed between young and older adults.[35] Similar to the observed sex-discrepancy, we suspect this observation is also partly due to a normal physiologic variation. There are some reported differences in albumin excretion between children and adults. For example, while overweight and obesity are likely to lead to an increasing prevalence of kidney and cardiovascular disease in later life, in childhood they are paradoxically associated with a lower urine ACR.[13, 14] This is in keeping with other counter-intuitive relationships at this age, eg obese children showing apparently better flow-mediated dilatation.[36] There is also some evidence to suggest that children have a greater orthostatic variation in albumin excretion than adults.[37] In addition to physiologic factors, there may be a pathologic component to the high urine ACR levels observed among some children. These two components will be difficult to delineate until there are follow-up data on the persistence or regression of albuminuria when participants reach adulthood, and ideally data on the cumulative incidence of downstream clinical events.

Nonetheless, the adult participants in our study had a higher prevalence of albuminuria than anticipated. This was driven mostly by a high prevalence of albuminuria among mothers, who comprised 85.5% of the adult cohort. While it is well established that average ACR values are higher among adult females, this does not always translate into a higher prevalence of albuminuria.[38] In our study the main reason for the observed sex-discrepancy in ACR was a lower median urine creatinine concentration among mothers, which explains their higher prevalence of albuminuria despite a slightly lower prevalence of risk-factors such as hypertension and obesity.[4, 39] Compared to our overall value of 13.5%, the 2011/13 Australian Health Survey reported a prevalence of albuminuria below 10% until the age of 65 years (using sex-adjusted thresholds),[35] and the earlier AusDiab study (2004) found a lower prevalence again (6.6%).[39] Overall, it does seem that the prevalence of albuminuria among Australians is increasing over time, consistent with Australians' increasing BMI[35, 39, 40] and with a lower 2008 prevalence of 8.1% in the United States on a single, random sample.[40]

The parent-child concordance in albumin and ACR were low, consistent with genomic data regarding the hereditability of ACR.[19, 20] Shared environmental risk factors are also likely to have contributed to this observation. It may be that familial concordance is only unmasked at older ages, in keeping with the higher familial clustering of albuminuria observed among sibling adults in the Framingham study.[19] For children, this weak inter-generational concordance suggests that family history in itself will be insufficient to identify at-risk individuals and that additional risk factors will need to be considered if when developing screening and intervention strategies.

Meaning and implications for clinicians and policymakers: Our results have implications for the determination of albuminuria thresholds in children and adults. For children, thresholds may need to be increased and sex-stratified for random, single-measurement, spot urine ACR. Repeated, first-morning and/or timed samples may be necessary to accurately separate children at-risk of future kidney and cardiovascular events from those with physiologically higher ACR. For the adult cohort of CheckPoint, it is hard to reconcile a higher prevalence of albuminuria among mothers (here driven largely by a lower urine creatinine concentration) when females on average have a lower risk of cardiovascular and kidney disease at any given age.[42 43] This suggests limitations in the thresholds currently used to define albuminuria, which have been derived based on the average urine ACR value required to meet the definition of an abnormal albumin excretion rate.[25] While this might appear to be a reasonable approach, the definition of an abnormal albumin excretion rate is based on limited distribution data and studies relating albumin excretion to the future development of diabetic nephropathy as defined by the development of a positive urine dipstick result.[44-48] New ACR thresholds could perhaps be defined by such data directly relating ACR to the risk of cardiovascular or kidney disease. However, this would increase the numbers identified as having albuminuria, thus if applied to clinical practice this runs the risk of generating overdiagnosis in people who are unlikely to benefit from treatment where trial data are limited, as is the case here.[16, 17, 49] It is also important to remember that a constant relative risk for a biomarker across its normal range does not equate to a constant risk difference, and there may not be a clinically meaningful increase in events or net-benefit to treatment at lower levels.[17]

Unanswered questions and future research: In summary, the prevalence of albuminuria among adult Australians is concerning with regards to their risk of future cardiovascular and kidney disease. Given this, and that specific treatments already exist (angiotensin converting

enzyme inhibitors and angiotensin receptor blockers), we need trials to determine if the treatment of isolated albuminuria is beneficial, at what threshold, and if treatment targets for patients with concomitant hypertension should include urine ACR. Albuminuria is common among Australian children as determined by the measurement of urine ACR on randomly timed, spot urine collection. However, more research is required into threshold selection for children and this requires prospective data tying urine ACR to future clinical events.

ACKNOWLEDGEMENTS: This paper uses unit record data from Growing Up in Australia, the Longitudinal Study of Australian Children. The study is conducted in partnership between the Department of Social Services (DSS), the Australian Institute of Family Studies (AIFS) and the Australian Bureau of Statistics (ABS). The findings and views reported in this paper are those of the author and should not be attributed to DSS, AIFS or the ABS. REDCap (Research Electronic Data Capture) electronic data capture tools[50] were used in this study. More information about this software can be found at: www.project-redcap.org. We thank the LSAC and CheckPoint study participants, staff and students for their contributions.

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the study, but played no role in the conduct or analysis of the trial. DSS played a role in study design; however, no other funding bodies had a role in the study design and conduct; data collection, management, analysis, and interpretation; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

CONTRIBUTIONS: NL, SK, JC, AG, DB, KL, MW and JCC provided critical input into the design of this component of the Child Health CheckPoint study, analysis and interpretation of the study data, and manuscript preparation. NL wrote the first draft of the manuscript. AG performed the statistical analysis. MW is the Principal Investigator of the Child Health CheckPoint.

DATA SHARING STATEMENT: Dataset and technical documents are available from *Growing Up in Australia*: The Longitudinal Study of Australian Children via low-cost license for bone fide researchers. More information is available at www.growingupinaustralia.gov.au

FIGURE CAPTIONS AND FOOTNOTES:

Figure 1: Participant flow chart

n=number of families, c=number of children, p=number of attending adults, MAC=Main assessment centre, mAC=Mini assessment centre, HV=Home visit assessment, LSAC=Longitudinal Study of Australia Children.

*Unable to analyse due to insufficient volume of poor quality sample

^Data excluded from 2 children and 1 parent with ACR>200mg/mmol or Albumin>2000mg/L, and data from 15 non-biological child-parent pairs excluded from concordance analyses.

Figure 2: Density plots for urine measures

— Girls/Mothers; — Boys/Fathers; - - - All.

mg: milligrams; mmol: millimoles; L: litres.

Graphs plot log-transformed data, with x-axes labelled using actual values for ease of interpretation.

Figure 3: Parent-child pair scatter plots

mg: milligrams; mmol: millimoles; L: litres.

Graphs plot log-transformed data, with x-axes labelled using actual values for ease of interpretation.

SUPPLEMENTARY DOCUMENT DESCRIPTIONS: supplementary appendix containing Supplementary table S1a: Percentile data for urine measures by sex

Supplementary table S1b: Percentile data for urine measures overall for each age cohort

Supplementary table S2a: Mother-child concordance

Supplementary table S2b: Father-child concordance

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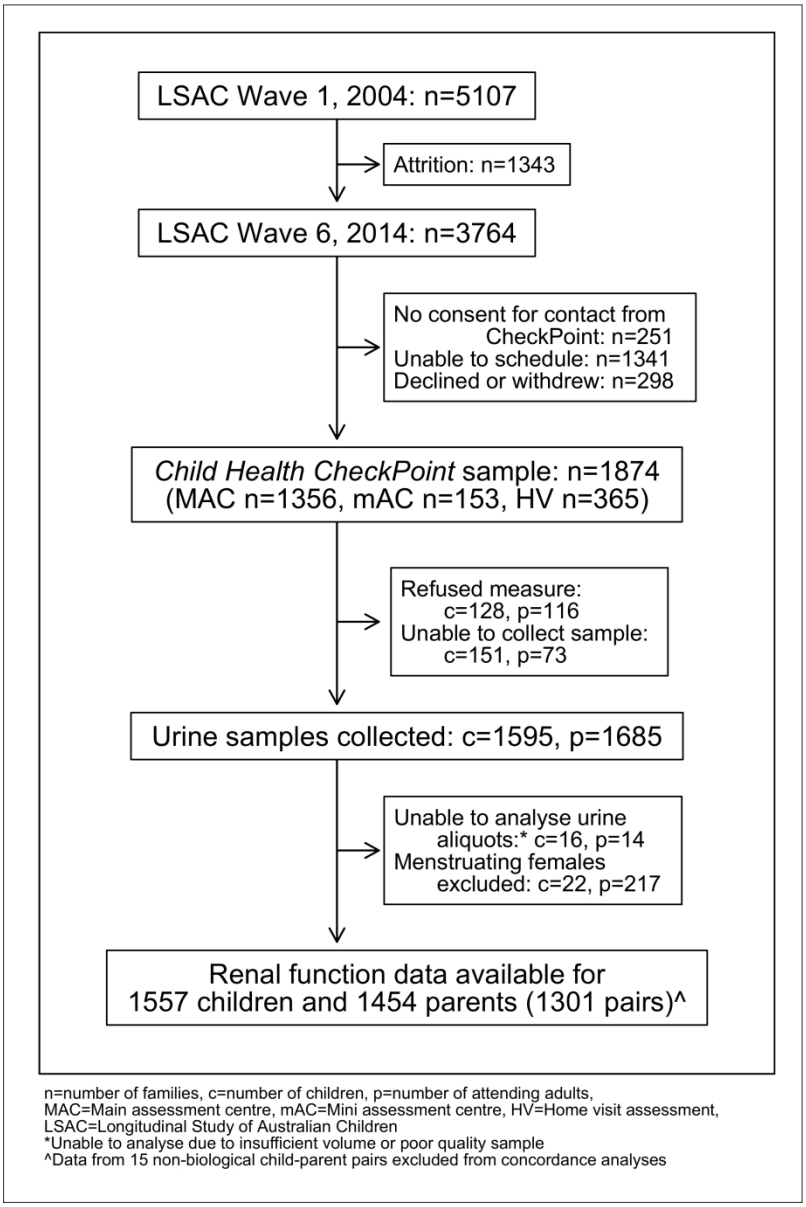

Figure 1: Participant flow chart
n=number of families, c=number of children, p=number of attending adults, MAC=Main assessment centre, mAC=Mini assessment centre, HV=Home visit assessment, LSAC=Longitudinal Study of Australia Children.
*Unable to analyse due to insufficient volume of poor quality sample
^Data excluded from 2 children and 1 parent with ACR>200mg/mmol or Albumin>2000mg/L, and data from 15 non-biological child-parent pairs excluded from concordance analyses.

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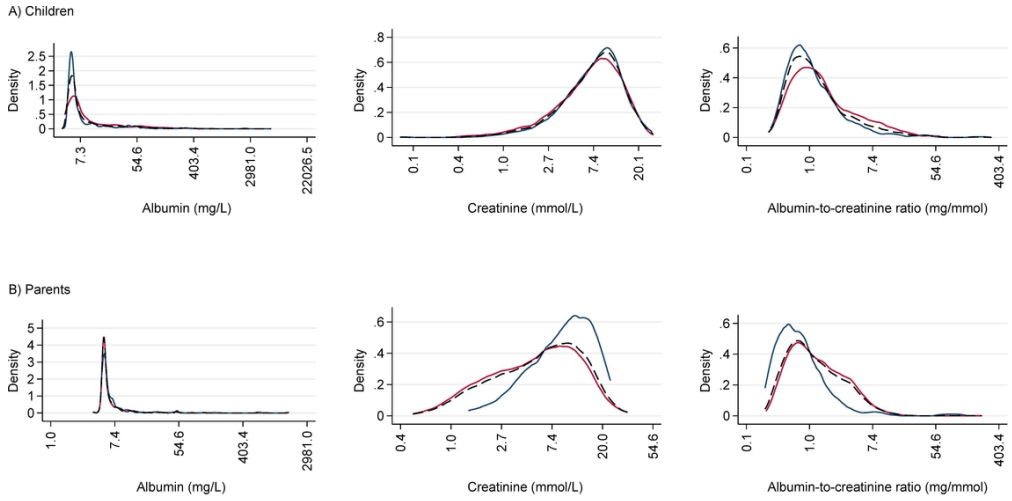

Figure 2: Density plots for urine measures
Red line: Girls/Mothers; Blue line: Boys/Fathers; Black, dotted line: All.
mg: milligrams; mmol: millimoles; L: litres.
Graphs plot log-transformed data, with x-axes labelled using actual values for ease of interpretation.

96x47mm (300 x 300 DPI)

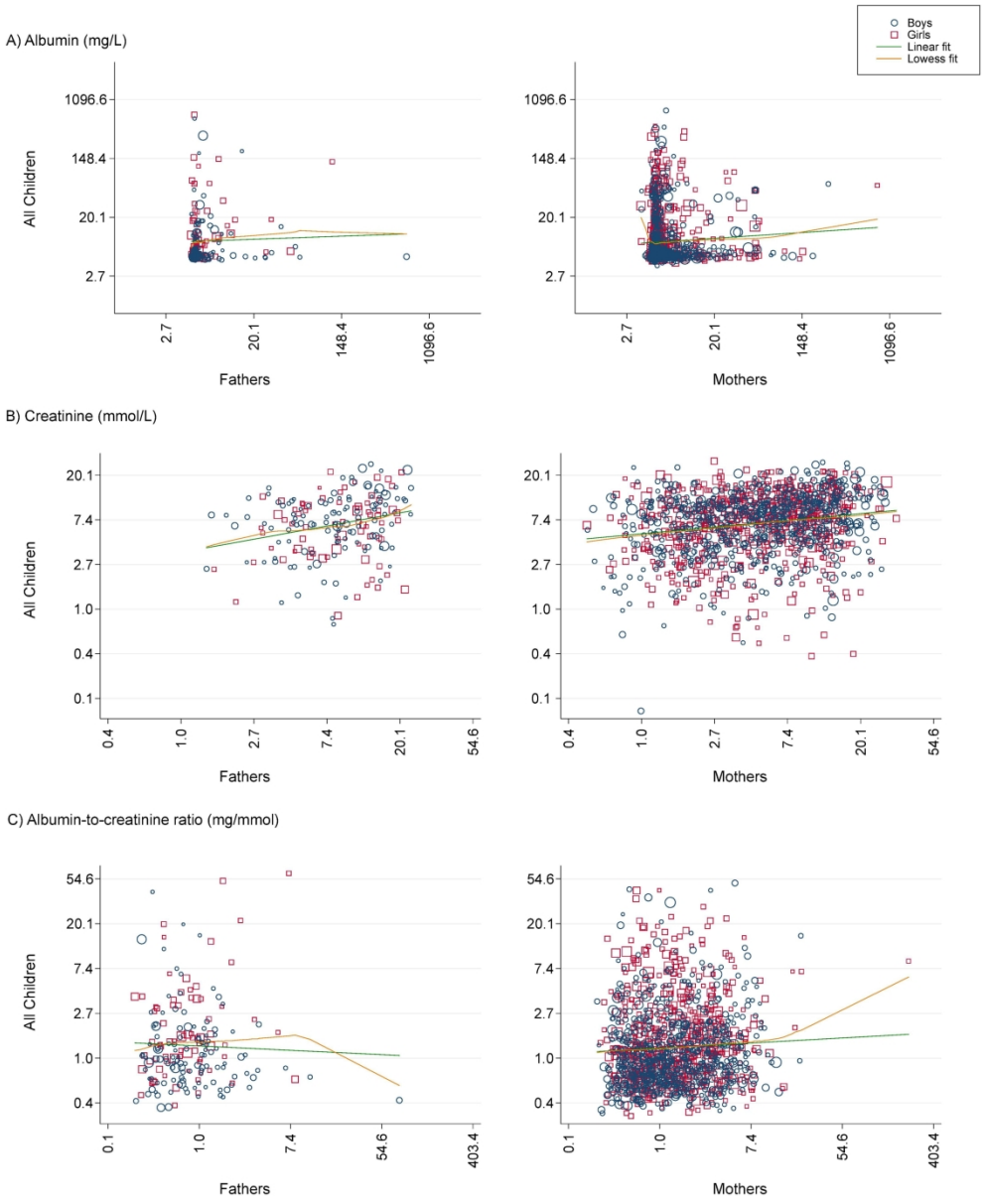

Figure 3: Parent-child pair scatter plots
mg: milligrams; mmol: millimoles; L: litres.
Graphs plot log-transformed data, with x-axes labelled using actual values for ease of interpretation.

221x270mm (300 x 300 DPI)

Supplementary tables S1a. Percentile data for urine measures by sex

	Male							Female						
Variable	**P5**	**P10**	**P25**	**P50**	**P75**	**P90**	**P95**	**P5**	**P10**	**P25**	**P50**	**P75**	**P90**	**P95**
Children														
Albumin (mg/L)	4.94	5.04	5.26	5.63	7.62	25.98	51.11	5.04	5.16	5.42	6.74	13.18	50.76	88.45
Creatinine (mmol/L)	2.07	2.99	5.00	8.03	11.31	15.09	17.84	1.56	2.59	4.49	7.65	11.33	15.05	17.27
Albumin creatinine ratio	0.42	0.47	0.61	0.90	1.65	3.55	6.03	0.45	0.52	0.71	1.20	2.65	6.93	10.82
Adults														
Albumin (mg/L)	4.97	5.06	5.22	5.50	6.60	9.13	20.73	4.91	5.01	5.18	5.42	6.38	10.57	17.24
Creatinine (mmol/L)	2.72	3.78	5.95	9.65	14.82	19.05	20.50	1.10	1.48	2.68	5.88	10.34	14.56	17.51
Albumin creatinine ratio	0.29	0.34	0.41	0.66	1.05	1.96	3.28	0.39	0.46	0.63	1.13	2.33	4.22	5.78

Supplementary tables S1b. Percentile data for urine measures overall for each age cohort

Variable	**P5**	**P10**	**P25**	**P50**	**P75**	**P90**	**P95**
Children							
Albumin (mg/L)	4.96	5.09	5.31	5.91	9.83	33.66	68.69
Creatinine (mmol/L)	1.79	2.76	4.74	7.88	11.32	15.05	17.32
Albumin creatinine ratio	0.43	0.48	0.65	1.03	1.97	4.82	8.96
Adults							
Albumin (mg/L)	4.92	5.02	5.19	5.43	6.43	10.51	17.24
Creatinine (mmol/L)	1.16	1.59	3.00	6.41	11.16	15.31	18.60
Albumin creatinine ratio	0.37	0.42	0.60	1.01	2.09	4.02	5.40

Supplementary table S2a. Mother-child concordance

Variable	Boys			Girls		
Pearson's Correlation	**N**	**CC**	**95% CI**	**N**	**CC**	**95% CI**
Albumin (mg/L)	588	0.04	-0.05 to 0.12	523	0.07	-0.01 to 0.16
Creatinine (mmol/L)	589	0.23	0.15 to 0.30	523	0.16	0.07 to 0.24
Albumin creatinine ratio	588	0.09	0.01 to 0.17	523	0.08	0.00 to 0.17
Multivariable Linear Regression*	**N**	**RC**	**P-value**	**N**	**CC**	**95% CI**
Albumin (mg/L)	586	0.03	0.7	520	0.12	0.1
Creatinine (mmol/L)	587	0.17	<0.001	520	0.13	0.002
Albumin creatinine ratio	586	0.10	0.01	520	0.09	0.09
Partial correlation coefficient*	**N**	**RC**		**N**	**CC**	
Albumin (mg/L)	586	0.02		520	0.07	
Creatinine (mmol/L)	587	0.21		520	0.1	
Albumin creatinine ratio	586	0.10		520	0.07	

CC: correlation coefficient; RC: estimated regression coefficient; CI: confidence interval

* Adjusted for parent age, Index of Relative Socioeconomic Disadvantage, child and parent body mass index, parent and child sex. Albumin, creatinine and albumin creatinine ratio have been log transformed.

Supplementary table S2b. Father-child concordance

Variable	Boys			Girls		
Pearson's Correlation	**N**	**CC**	**95% CI**	**N**	**CC**	**95% CI**
Albumin (mg/L)	117	0.00	-0.18 to 0.18	72	0.20	-0.04 to 0.41
Creatinine (mmol/L)	117	0.26	0.08 to 0.42	72	0.13	-0.11 to 0.35
Albumin creatinine ratio	117	-0.16	-0.33 to 0.03	72	0.26	0.03 to 0.46
Multivariable Linear Regression*	**N**	**RC**	**P-value**	**N**	**CC**	**95% CI**
Albumin (mg/L)	114	0.05	0.7	72	0.43	0.07
Creatinine (mmol/L)	114	0.31	0.004	72	0.18	0.3
Albumin creatinine ratio	114	-0.18	0.08	72	0.38	0.03
Partial correlation coefficient*	**N**	**RC**		**N**	**CC**	
Albumin (mg/L)	114	0.04		72	0.22	
Creatinine (mmol/L)	114	0.28		72	0.14	
Albumin creatinine ratio	114	-0.17		72	0.27	

CC: correlation coefficient; RC: estimated regression coefficient; CI: confidence interval.

* Adjusted for parent age, Index of Relative Socioeconomic Disadvantage, child and parent body mass index, parent and child sex. Albumin, creatinine and albumin creatinine ratio have been log transformed.

STROBE Statement—checklist of items that should be included in reports of observational studies
Paper title: Albuminuria: Population epidemiology and concordance in 11-12 year old Australians and their parents
Person completing checklist: Nicholas Larkins

	Item No	Recommendation	Page number
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up ~~*Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale~~ for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5
		~~(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed~~ ~~*Case-control study*—For matched studies, give matching criteria and the number of controls per case~~	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6, 7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6, 7
Bias	9	Describe any efforts to address potential sources of bias	6, 7
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6, 7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	7
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed ~~*Case-control study*—If applicable, explain how matching of cases and controls was addressed~~	NA

~~*Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy~~	
(*e*) Describe any sensitivity analyses	NA

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	Figure 1
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10
		(b) Indicate number of participants with missing data for each variable of interest	Table 2
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	NA
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	12
		Cross-sectional study—Report numbers of outcome events or summary measures	12
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	12
		(*b*) Report category boundaries when continuous variables were categorized	6 Table 2
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15, 16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	16
Generalisability	21	Discuss the generalisability (external validity) of the study results	16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Albuminuria: Population epidemiology and concordance in 11-12 year old Australians and their parents

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Albuminuria: Population epidemiology and concordance in 11-12 year old Australians and their parents

Larkins NG,[1-3] Kim S,[1,4] Carlin J,[5,6] Grobler AC,[5] Burgner DP,[5,7,8] Lange K,[5] Craig JC,[1,2] Wake M.[5,9]

Affiliations: [1] Centre for Kidney Research, The Children's Hospital at Westmead, Westmead, NSW, Australia; [2] School of Public Health, University of Sydney, Sydney, NSW, Australia; [3] Department of Nephrology, Princess Margaret Hospital, Subiaco, WA, Australia; [4] School of Women's and Children's Health, University of New South Wales, Sydney, NSW, Australia; [5] Murdoch Children's Research Institute, Royal Children's Hospital, Parkville, VIC, Australia; [6] Melbourne School of Population and Global Health, Faculty of Medicine, Dentistry and Health Services, University of Melbourne, Parkville, VIC, Australia; [7] Department of Paediatrics, The University of Melbourne, Melbourne, VIC, Australia; [8] Department of Paediatrics, Monash University, Melbourne, VIC, Australia; [9] Department of Paediatrics & The Liggins Institute, The University of Auckland, Auckland, New Zealand.

Correspondence to: Professor Melissa Wake
Murdoch Children's Research Institute
The Royal Children's Hospital
50 Flemington Road, Parkville 3052, VIC Australia
T: +61 3 9345 5761
E: melissa.wake@mcri.edu.au

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Abbreviations: ACR: albumin-to-creatinine ratio; AHS: Australian Health Survey; BMI: body mass index; CC: Pearson's correlation coefficient; CheckPoint: Child Health CheckPoint; CI: confidence interval; IQR: interquartile range; Disadvantage Index: Index of Relative Socio-economic Disadvantage; KDIGO: Kidney Disease Improving Global

Outcomes; L: litres; LSAC: Longitudinal Study of Australian Children; mg: milligrams; mmol: millimoles; n: number in category; N: number with valid data for characteristic; NHANES: National Health and Nutrition Examination Survey; RC: estimated regression coefficient; SD: standard deviation.

ABSTRACT

Objectives: To describe the distribution of albuminuria among 11 to 12-year old Australian children and their parents, and assess its intergenerational concordance within parent-child dyads.

Design: Population-based cross-sectional study (the Child Health CheckPoint), nested within the Longitudinal Study of Australian Children.

Setting: Assessment centres (seven Australian cities and eight regional towns) and home visits across Australia, February 2015 to March 2016.

Participants: Of all participating CheckPoint families (n=1874), 1557 children (46.2% girls) and 1454 parents (85.5% mothers) provided random urine samples at the visit; samples from menstruating females were excluded.

Outcome measures: Urine albumin-to-creatinine ratio (ACR) and its components (urine albumin and creatinine concentration); albuminuria was defined as an ACR ≥3.4 mg/mmol. Pearson's correlation coefficients and multivariable linear regression models assessed parent-child concordance, using log-transformed data due to skewing. Survey weights and methods were applied to account for the complex sample design.

Results: The median ACR for children was 1.03 mg/mmol (interquartile range (IQR) 0.65 to 1.97) and 1.01 mg/mmol (IQR 0.60 to 2.09) for adults. The median ACR was higher in girls (1.20, IQR 0.71 to 2.65) than boys (0.90, IQR 0.61 to 1.65) and in mothers (1.13, IQR 0.63 to 2.33) than fathers (0.66, IQR 0.41 to 1.05). Albuminuria was detected in 15.1% of children (girls 20.8%, boys 10.1%) and 13.5% of adults (15.1% mothers, 4.0% fathers) had albuminuria. There was a small correlation between parent and child ACR (Pearson correlation coefficient 0.06, 95% confidence interval 0.01 to 0.12).

Conclusions: Albuminuria is common among Australian children and adults, which is of concern because it predicts risk for kidney and cardiovascular disease, and mortality. The weak concordance among inter-generational pairs for urine ACR suggests either that genetic hereditability is low or that it becomes evident only at later offspring life stages.

Strengths and limitations of this study

- Australia-wide population-based cohort sampled using a multi-stage, clustered survey design allowing for the derivation of accurate population-level estimates.
- Large sample of biological parent-child pairs allowing for precise estimates of intergenerational concordance.
- First morning or timed urine samples were not available to investigate the impact of orthostatic variation on urine ACR. The estimates of prevalence would be lower if participants with intermittent proteinuria were identified and excluded.
- The single (rather than repeated) urine ACR value makes the study open to residual measurement error.

INTRODUCTION

Albuminuria, even at low levels, is an important marker of chronic kidney disease and strongly predicts end-stage kidney disease.[1 2] It also independently predicts cardiovascular events and all-cause mortality, probably as a reflection of endothelial dysfunction.[3] There are different methods of measuring albuminuria. The reference standard, 24-hour urine collection, is impractical in many settings, so that spot urine albumin-to-creatinine ratio (ACR) is routinely used in clinical practice. Urine ACR and spot urine albumin concentration reliably estimate 24-hour albumin excretion, although the correlation is stronger for ACR because it accounts for differences in urine concentration due to hydration status.[4] There are also postural changes in albumin excretion.[5] However, because the timing of collection tends not to correlate with explanatory variables of interest (eg socio-economic status or age) this does not introduce confounding. Consequently, random samples are routinely used for research purposes also and most evidence relating albuminuria to kidney and cardiovascular risk derives from random urine ACR.[6]

Despite the potential utility of urine ACR as a cheap, non-invasive biomarker, data about the distribution of ACR and its components in children are mostly limited to disease-specific contexts.[7] Thus, its applicability as a marker of risk in well children is unknown. Nonetheless, it has been widely adopted because its ease of collection makes it feasible to bring children's kidney health into population studies. In children with type 1 diabetes mellitus, persistent or intermittent microalbuminuria predicts the future development of macroalbuminuria, and in children with renal dysplasia or glomerular pathology albuminuria is also predictive of long-term renal function.[8-12] However, the population-based data that are available in children suggest some important discrepancies compared to adults. For example, whereas obese adult have higher rates of albuminuria, the reverse has been reported in children (an odds ratio of 0.34 for albuminuria in overweight and obese compared to normal weight children).[13] In addition, orthostatic proteinuria, generally considered to be a benign condition, may affect up to 20% of children 9 to 16 years old.[13-15]

Among adults, given the clear relationship between albuminuria and future cardiovascular events or chronic kidney disease, there has been a shift in focus from pathological levels to the risk associated with urine ACR levels in the low-normal range. The Chronic Kidney Disease Prognosis Consortium has shown through collaborative meta-analysis that a urine ACR of 1.1 mg/mmol is associated with a hazard ratio of 1.20 for all-cause mortality (95% confidence interval [CI] 1.15 to 1.26) compared to a urine ACR of 0.6 mg/mmol.[6] Such relationships,

where risk extends below traditional thresholds into the normal range, are common among clinical biomarkers and make it difficult to define the threshold at which values should be considered abnormal.[16 17]

It is increasingly recognised that the development of chronic diseases, such as kidney and cardiovascular disease, begins in early life.[18] Through the study of parent-child concordance for early disease markers or risk factors, we can begin to understand the role of inherited genetic and environmental influences in establishing adverse lifecourse trajectories. A sub-study of the Framingham Heath Study involving 1055 adult participants found up to 20% of the population variance in urine ACR may be due to genetic hereditability.[19] Single nucleotide polymorphism data also suggests a genetic component to albuminuria.[20] If concordance is confirmed while offspring are still children, this could provide useful prognostic information early in life as we attempt to develop strategies allowing the earlier identification of people progressing towards disease states, with the ultimate goal of providing earlier interventions to keep people healthy.

The Child Health CheckPoint study nested within *Growing Up in Australia* (also known as the Longitudinal Study of Australian Children, LSAC) provides an important opportunity to examine these issues. We aimed to assess the cross-sectional distribution of urine ACR and related metrics in Australian children aged 11-12 years and their parents, and describe the extent of intergenerational concordance for this measure.

METHODS

Study design and participants: Details of the initial LSAC study design and recruitment are outlined elsewhere.[21 22] In brief, LSAC recruited a nationally representative sample of 5107 infants using a 2-stage random sampling design with postcode as the primary sampling unit, and followed them up in biennial 'waves' of data collection up to 2015. The initial proportion recruited to the relevant B cohort in 2004 was 57.2%, of whom 73.7% (n=3764) were retained to LSAC wave 6 in 2014.

At the wave 6 visit, all remaining families (n=3513) were invited to consent to their contact details being shared with the Child Health CheckPoint (CheckPoint) team. In 2015, families that consented were then sent an information pack via post and received an information and recruitment phone call. The CheckPoint's detailed cross-sectional biophysical assessment, nested between LSAC waves 6 and 7 (aged 11-12 years), took place between February 2015 and March 2016. 1874 families participated. A more detailed description of the CheckPoint study design is available elsewhere.[23 24]

Ethics and Consent: The CheckPoint study protocol was approved by The Royal Children's Hospital Melbourne Human Research Ethics Committee (33225D) and Australian Institute of Family Studies Ethics Committee (14-26). The attending parent provided written informed consent for themself and their child to participate in the study.

Patient and Public Involvement: Because LSAC is a population-based longitudinal study, no patient groups were involved in its design or conduct. To our knowledge, the public was not involved in the study design, recruitment or conduct of LSAC study or its CheckPoint module. Parents received a summary health report for their child and themselves at or soon after the CheckPoint assessment visit. They consented to take part knowing that they would not otherwise receive individual results about themselves or their child.

Procedure: Urine was collected at a specialised 3.5 hour (major and large cities) or 2.5 hour (smaller regional centres) CheckPoint assessment centre visits; those families (n=378) who could not attend were offered a shorter home visit (figure 1). Child Health CheckPoint assessments took place between Feb 2015 and March 2016. As assessment centre visits ran throughout the day, sample collection time could be anywhere between 9 am and 6 pm, even though urine collection was requested as part of the first assessment station after check-in. Participants were asked to urinate directly into a polypropylene sterile pot until full (or as best possible), and included in current analyses if they provided a usable sample (figure 1). Results from mothers and girls who self-reported they were menstruating were excluded. Only biological parent-child pairs were included for concordance analysis.

Outcome measure: Urine samples were stored at 4^{o}C until processing (77% of samples processed within three hours and 85% within 13 hours; maximum seven days for home visit participants). They were then pipetted under laboratory conditions into a maximum of 12 x 0.7 mL aliquots and frozen and stored at -80^{o}C. Analysis was performed at the Laboratory of the Baker Heart and Diabetes Institute. Samples were first defrosted over 30 minutes and then centrifuged at 500 rpm for three minutes. A Cobas Integra ® 400 plus analyzer performed the measurements, determining albumin using an immunoturbimetric assay and creatinine using the enzymatic colorimetric method. The lower limit for the detection of urine albumin on this machine is 3 mg/L and for urine creatinine is 0.1 mmol/L.

For descriptive purposes ACR was categorised according to the Kidney Disease Improving Global Outcomes (KDIGO) 2012 guidelines: microalbuminuria 3.4 to 34 mg/mmol and macroalbuminuria >34 mg/mmol.[25] We also determined the prevalence of albuminuria among

adults using the current Australian guidelines: microalbuminuria in fathers 2.5 to 25 mg/mmol and macroalbuminuria in fathers >25 mg/mmol, microalbuminuria in mothers 3.5 to 35 mg/mmol and macroalbuminuria in mothers >35 mg/mmol.[26] For purposes of this paper, we used the overarching term 'albuminuria' to refer to the combined participants with micro- or macroalbuminuria.

Potential confounders:

Disadvantage score: In Australia, Socio-Economic Indexes for Areas provide standardised scores for socioeconomic position by geographic area (postcode of family domicile) compiled from 2011 Australian Census data. We used the Index of Relative Socioeconomic Disadvantage (disadvantage index) which numerically summarises the social and economic conditions of Australian neighbourhoods (national mean of 1000 and standard deviation of 100, where higher values represent less disadvantage).[27]

Anthropometry: Height was measured twice, three times where the first two measures differed by >0.5 cm, without shoes or socks using a portable rigid stadiometer (model 10955, Invicta, United Kingdom), and all measurements averaged to produce the final value. An electronic, calibrated scale (lnBody230 scales, Biospace Co. Ltd., South Korea) was used to measure body weight with participants wearing light clothing and no shoes or socks. Body mass index (BMI) for children was converted to z-scores according to the 2000 Centre for Disease Control and Prevention growth charts.[28] Overweight was defined as BMI ≥85th centile and <95th centile, and obesity as BMI ≥95th centile.[29] A steel tape measure was used to measure waist circumference using the cross-hand technique at the narrowest point (or mid-point if no narrowing) between then 10th rib and the top of the iliac crest. Two measurements were taken provided these were within 0.1 cm, otherwise a third measurement was performed. The final value was the mean of the two closest measurements.

Blood pressure: Blood pressure was measured at the brachial artery using an oscillometric device (SphygmoCor XCEL, AtCor Meidcal Pty. Ltd., Australia), following at least 7 minutes of rest, in the supine position. Three measurements were taken with at least one minute of rest between readings. The final value was the average of all three measurements. Hypertension and high-normal blood pressure were defined as a height, sex and age adjusted blood pressure centile ≥95th centile or <95th but ≥90th centile respectively, using the Fourth Report from the National High Blood Pressure Education Program reference thresholds.[30 31]

Other: Medical history was by obtained by self- or guardian-report. Pubertal status was determined using self-reported responses on the Pubertal Development Scale.[32]

Statistical Analysis: Concordance between parents and children was assessed by: 1) Pearson's correlation coefficients with 95% confidence intervals; and 2) linear regression with child variable as dependent variable and parent variable as independent variable. Linear regression models were adjusted for parent age, Disadvantage Index, and parent and child BMI and sex in models including both sexes. In addition, the Pearson's correlation coefficient and linear regression analyses were repeated using weighted multi-level survey analyses. These results were similar to the simple correlations and regression results adjusted for stratification and clustering by postcode only, and only the simple results are reported. Two children and one adult showed an ACR >200 mg/mmol or urine albumin concentration >2000 mg/L. These were included in the distribution statistics consistent with the population-based sampling and aims. However, they were excluded from the concordance analyses because they were outliers and influential observations, considered to represent discrete glomerular pathology.

Population summary statistics and proportions were estimated by applying survey weights and survey procedures that corrected for sampling and participation biases and took into account clustering in the sampling frame. Standard errors were calculated taking into account the complex design and weights.[33] More detail on the calculation of weights is provided elsewhere.[34]

The differences between adult and child, and between male and female, groups were tested for statistical significance using linear or logistic regression. All urine variables were log-transformed for the purposes of hypothesis testing and concordance analysis, due to severe right skewing.

RESULTS

Sample characteristics: Of the 1874 families assessed, 1557 children (83.1%) and 1454 adults (90.0%) contributed valid urine samples for analysis (1301 biological parent-child pairs; figure 1). 22 children and 217 adults were excluded because they were menstruating, and 15 carer-child pairs were excluded from concordance analysis because the adult was a non-biological parent. There were slightly more boys (n=837, 53.8%) than girls (n=720) and most parents were mothers (n=1243, 85.5%) (table 1).

Table 1. Participant characteristics; all values are n (%) except age

Characteristic	Boys			Girls			Fathers			Mothers†		
	n	N	%*	n	N	%*	n	N	%*	n	N	%*
Age (years), mean* (SD)	835	12.0	0.38	720	12.0	0.42	211	462	6.89	1243	43.5	5.35
BMI category												
Overweight	127	836	16.3	107	720	16.8	90	214	42.9	382	1237	31.2
Obese	84	836	12.7	59	720	9.6	71	214	37.2	382	1237	32.4
Blood pressure category												
High-normal	18	787	2.5	26	692	4.1	111	197	57.0	372	1164	32.7
Hypertensive	24	787	4.9	22	692	3.6	31	197	18.1	88	1164	7.8
Socio-economic status quintile												
1st (most disadvantaged)	70	833	13.4	54	719	10.6	17	203	11.9	93	1242	12.2
2nd	128	833	19.6	107	719	17.9	37	203	22.6	181	1242	17.6
3rd	145	833	19.8	134	719	20.6	40	203	23.3	225	1242	20.3
4th	194	833	21.8	179	719	25.1	37	203	15.8	317	1242	24.8
5th (least disadvantaged)	296	833	25.5	245	719	25.8	77	203	26.4	426	1242	25.1
Diabetes	2	837	0.2	3	720	0.6	9	215	4.8	26	1243	2.6
Heart condition	-	-	-	-	-	-	9	211	5.4	24	1243	2.7
Started puberty	686	793	87.8	629	663	94.8	-	-	-	-	-	-

SD: standard deviation; BMI: body mass index; n: number in category; N: number with valid data for characteristic (denominator).
* weighted mean/percentage; † 98.9% of adult participants were biologic parents of participating children.

The participant characteristics were broadly reflective of the Australian population, as per the study design, with the exception that the sample was relatively less disadvantaged than the general population (25.6% of children in the least but only 12.1% in the most disadvantaged national quintile). Consistent with this, most adults and over one quarter of children were overweight or obese (65.9% adults, 27.8% children). There were no major differences in participant characteristics by sex for the childhood cohort. However, mothers were on average younger than fathers (43.5 years vs 46.7 years), fewer had a high-normal BP or hypertension (40.5% vs 75.1%), and fewer were overweight or obese (63.6% vs 80.1%).

Distribution of ACR and albuminuria (table 2 and figure 2):

Children: The median ACR among children was 1.03 mg/mmol (IQR 0.65 to 1.97) (table 2).

Table 2. Distribution of urine albumin, creatinine, albumin to creatinine ratio and albuminuria by age cohort and sex

Variable	Males		Females		All	
	N	Median (IQR)	N	Median (IQR)	N	Median (IQR)
Children						
Albumin (mg/L)	837	5.6 (5.3 to 7.6)	720	6.7 (5.4 to 13)	1557	5.9 (5.3 to 9.8)
Creatinine (mmol/L)	837	8.0 (5.0 to 11.3)	720	7.7 (4.5 to 11)	1557	7.9 (4.7 to 11.3)
Albumin creatinine ratio	837	0.9 (0.6 to 1.7)	720	1.2 (0.7 to 2.7)	1557	1.0 (0.7 to 2.0)
Adults						
Albumin (mg/L)	211	5.5 (5.2 to 6.6)	1243	5.4 (5.2 to 6.4)	1454	5.4 (5.2 to 6.4)
Creatinine (mmol/L)	211	9.7 (6.0 to 14.8)	1243	5.9 (2.7 to 10.3)	1454	6.4 (3.0 to 11.2)
Albumin creatinine ratio	211	0.7 (0.4 to 1.1)	1243	1.1 (0.6 to 2.3)	1454	1.0 (0.6 to 2.1)
	n/N	**%‡**	**n/N**	**%‡**	**n/N**	**%‡**
Children						
Albuminuria*	92/837	10.1	141/720	20.8	233/1557	15.1
Microalbuminuria	85/837	9.5	135/720	20.0	220/1557	14.2
Macroalbuminuria	7/837	0.9	6/720	0.9	13/1557	0.9
Adults						
Albuminuria	9/211	4.0	188/1243	15.1	197/1454	13.5
Microalbuminuria	7/211	2.9	187/1243	15.0	194/1454	13.3
Macroalbuminuria	2/211	1.1	1/1243	<0.1	3/1454	0.2
Albuminuria (sex-corrected)†	15/211	6.9	179/1243	14.3	194/1454	13.3
Microalbuminuria (sex-corrected)	13/211	5.8	178/1243	14.3	191/1454	13.1
Macroalbuminuria (sex-corrected)	2/211	1.1	1/1243	<0.1	3/1454	0.2

IQR: interquartile range; n: number in category; N: number with valid data for characteristic (denominator); mg: milligrams; mmol: millimoles; L: litres.
* combined total of micro- and macroalbuminuria; † using current Australian thresholds to define albuminuria, 2.5 mg/mmol for fathers and 3.5 mg/mmol for mothers; ‡ weighted percentage.

The median urine albumin concentration for boys was 5.6 mg/L (IQR 5.3 to 7.6) and for girls was 6.7 mg/L (IQR 5.4 to 13.2; p<0.001). Albuminuria was present in 15.1% of children, and albuminuria was more common in girls than boys (20.8% versus 10.1%; p<0.001), largely due to differences in urine albumin as opposed to urine creatinine concentration (figure 2). Mean (standard deviation) data, and log-transformed data are presented in supplementary table S1. Percentile values for urine albumin, creatine and albumin-to-creatinine ratio distributions are presented in supplementary tables S2a and S2b.

Adults: The median ACR among adults was 1.01 mg/mmol (IQR 0.60 to 2.09). The prevalence of albuminuria was much higher in mothers than fathers, at 15.1% vs 4.0% respectively (p<0.001) for the KDIGO thresholds, and 14.3% vs 6.9% respectively (p=0.02) for the sex-stratified Australia thresholds, noting that the number of fathers on which this estimate was based was small. Among adults, the sex discrepancy in ACR was driven more by differences in the distribution of urine creatinine than urine albumin concentration (figure 2).

Intergenerational concordance of ACR: A weak positive correlation was present between biological parent and child urine ACR (r 0.06, 95% CI 0.01 to 0.12) and albumin (r 0.06, 95% CI 0.01 to 0.12), with stronger correlations for creatinine values (r 0.19, 95% CI 0.13 to 0.24) (figure 3). These values were essentially unchanged when using partial correlation coefficients to adjust for parent age, socio-economic status, and child and parent BMI and sex (table 3, sex-specific values shown in supplementary tables S3a and S3b). Multivariable linear regression showed some evidence of parent-child concordance for all three urine variables (table 3).

Table 3. Parent-child concordance

Variable			
Pearson's Correlation	**N**	**CC**	**95% CI**
Albumin (mg/L)	1300	0.06	0.01 to 0.11
Creatinine (mmol/L)	1301	0.19	0.13 to 0.24
Albumin creatinine ratio	1300	0.06	0.01 to 0.12
Multivariable Linear Regression*	**N**	**RC**	**P-value**
Albumin (mg/L)	1292	0.09	0.06
Creatinine (mmol/L)	1293	0.15	<0.001
Albumin creatinine ratio	1292	0.07	0.02
Partial correlation coefficient*	**N**	**RC**	
Albumin (mg/L)	1292	0.05	
Creatinine (mmol/L)	1293	0.18	
Albumin creatinine ratio	1292	0.07	

CC: Pearson's correlation coefficient; CI: confidence interval; mg: milligrams; mmol: millimoles; L: litres; RC: estimated regression coefficient.
* Adjusted for parent age, Index of Relative Socioeconomic Disadvantage, child and parent body mass index, parent and child sex. Albumin, creatinine and albumin creatinine ratio have been log transformed.

There was also a weak association between parent-child pairs for albuminuria (ACR ≥3.4 mg/mmol): in 73.3% of pairs neither parent or child had albuminuria, in 11.8% of pairs only the adult had albuminuria, in 12.8% of pairs only the child had albuminuria and in 2.0% both parent and child had albuminuria.

DISCUSSION

Principal findings: In this population-based Australian study, 13.5% of adults and 15.1% of children had albuminuria. The prevalence varied by sex, with albuminuria more common in females among both children and, especially, adults. In children the sex difference was mostly driven by an increased urine albumin concentration, whereas in adults the urine creatinine concentration was relatively more important. There was weak intergenerational concordance for urine albumin and ACR, but creatinine concordance was larger (0.15-0.19).

Strengths and limitations: Strengths of the Child Health CheckPoint study include the large sample size and the multi-stage, clustered survey methodology that together allow for the derivation of accurate population estimates. All samples were processed in a central research laboratory under strict protocols. The main weakness of the data presented here is that first morning or timed samples were not collected, and so we cannot account for the impact of orthostatic proteinuria. We also lacked the ability to account for day-to-day variability in urine ACR, which will result in residual measurement error.[35] Orthostatic proteinuria is a greater issue for children than adults and may have increased the prevalence estimates.[36] Sample attrition is a common limitation among long-running longitudinal studies. Retention in LSAC was similar to other birth-cohorts at this age.[37 38] Not all remaining families participated in CheckPoint. However, the sample remained similar to of the Australian population in most respects and survey weighting was used to account for drop-out and non-response among children.[24] There was an over-representation of mothers in the adult cohort, reducing the precision around estimates for fathers. The lack of longitudinal biospecimen data limits our ability to draw conclusions about the prevalence of albuminuria over time or investigate how this relates to future events.

Findings in relation to other studies: The prevalence of albuminuria among children was similar to other population-based studies. We recently performed an analysis of data from the 2011/13 Australian Health Survey (AHS) and found 12.8% of children aged 5 to 18 years had albuminuria using the same threshold of 3.4 mg/mmol.[13] In the United States, the prevalence of albuminuria in the National Health and Nutrition Examination Survey (NHANES) has been

reported as 8.9%.[14] However, in that study the mean age was 15.5 years, and older adolescents appear to have a lower prevalence of albuminuria.[13 39] In both the AHS and NHANES studies girls had a higher ACR than boys because of differences in urine albumin, rather than differences in urine creatinine concentration. We believe the most likely explanation for this is that normal physiologic values vary by sex, rather than sex-related differences in cardiovascular or kidney health at this age.

The prevalence of albuminuria and mean values for urine ACR, urine albumin and urine creatinine concentrations were similar in children and adults. This was unexpected because, as a marker of early disease and risk for future clinical cardiovascular and kidney events, we would expect an increase in the prevalence of albuminuria between childhood and mid-adulthood, as is observed between young and older adults.[40] Similar to the observed sex-discrepancy, we suspect this observation is also partly due to a normal physiologic variation. There are some reported differences in albumin excretion between children and adults. For example, while overweight and obesity are likely to lead to an increasing prevalence of kidney and cardiovascular disease in later life, in childhood they are paradoxically associated with a lower urine ACR.[13 14] This is in keeping with other counter-intuitive relationships at this age, eg obese children showing apparently better flow-mediated dilatation.[41] There is also some evidence to suggest that children have a greater orthostatic variation in albumin excretion than adults.[36] In addition to physiologic factors, there may be a pathologic component to the high urine ACR levels observed among some children. These two components will be difficult to delineate until there are follow-up data on the persistence or regression of albuminuria when participants reach adulthood, and ideally data on the cumulative incidence of downstream clinical events.

Nonetheless, the adult participants in our study had a higher prevalence of albuminuria than anticipated. This was driven mostly by a high prevalence of albuminuria among mothers, who comprised 85.5% of the adult cohort. While it is well established that average ACR values are higher among adult females, this does not always translate into a higher prevalence of albuminuria.[42] In our study the main reason for the observed sex-discrepancy in ACR was a lower median urine creatinine concentration among mothers, which explains their higher prevalence of albuminuria despite a slightly lower prevalence of risk-factors such as hypertension and obesity.[4 43] Compared to our overall value of 13.5%, the 2011/13 Australian Health Survey reported a prevalence of albuminuria below 10% until the age of 65 years (using sex-adjusted thresholds),[40] and the earlier AusDiab study (2004) found a lower prevalence

again (6.6%).[43] Overall, it does seem that the prevalence of albuminuria among Australians is increasing over time, consistent with Australians' increasing BMI[40 43] and with a lower 2008 prevalence of 8.1% in the United States on a single, random sample.[44]

The parent-child concordance in albumin and ACR were low, consistent with genomic data regarding the hereditability of ACR.[19 20] Shared environmental risk factors are also likely to have contributed to this observation. It may be that familial concordance is only unmasked at older ages, in keeping with the higher familial clustering of albuminuria observed among sibling adults in the Framingham study.[19] For children, this weak inter-generational concordance suggests that family history in itself will be insufficient to identify at-risk individuals and that additional risk factors will need to be considered if and when developing screening and intervention strategies.

Meaning and implications for clinicians and policymakers: Our results have implications for the determination of albuminuria thresholds in children and adults. For children, thresholds may need to be increased and sex-stratified for random, single-measurement, spot urine ACR. The current KDIGO guidelines acknowledge that the exclusion of patient-specific factors in defining albuminuria is controversial, but argue an ACR of 3.4 mg/mmol is more than three times the normal value (1 mg/mmol) in young adults and tied to risk regardless of age, sex, and ethnicity. Our data suggest that an ACR of 3.4 mg/mmol lies within the normal range for children, and there are also no data tying childhood ACR to future clinical events. Thus, the logic behind the exclusion of patient-specific factors cannot be applied to children and the use of a single threshold across all ages needs to be further explored. Repeated, first-morning and/or timed samples may be necessary to accurately separate children at-risk of future kidney and cardiovascular events from those with physiologically higher ACR. However, this must be balanced against the risk of excluding kidney markers from large population studies for which feasibility is paramount.

For the adult cohort of CheckPoint, it is hard to reconcile a higher prevalence of albuminuria among mothers (here driven largely by a lower urine creatinine concentration) when females on average have a lower risk of cardiovascular and kidney disease at any given age.[45 46] This suggests limitations in the thresholds currently used to define albuminuria, which have been derived based on the average urine ACR value required to meet the definition of an abnormal albumin excretion rate.[26] While this might appear to be a reasonable approach, the definition of an abnormal albumin excretion rate is based on limited distribution data and studies relating albumin excretion to the future development of diabetic nephropathy as defined by the

development of a positive urine dipstick result.[47-51] New ACR thresholds could perhaps be defined by such data directly relating ACR to the risk of cardiovascular or kidney disease. However, this would increase the numbers identified as having albuminuria, thus if applied to clinical practice this runs the risk of generating overdiagnosis in people who are unlikely to benefit from treatment where trial data are limited, as is the case here.[16 17 52] It is also important to remember that a constant relative risk for a biomarker across its normal range does not equate to a constant risk difference, and there may not be a clinically meaningful increase in events or net-benefit to treatment at lower levels.[17]

Unanswered questions and future research: In summary, the prevalence of albuminuria among adult Australians is concerning with regards to their risk of future cardiovascular and kidney disease. Given this, and that specific treatments already exist (angiotensin converting enzyme inhibitors and angiotensin receptor blockers), we need trials to determine if the treatment of isolated albuminuria is beneficial, at what threshold, and if treatment targets for patients with concomitant hypertension should include urine ACR. Albuminuria is common among Australian children as determined by the measurement of urine ACR on randomly timed, spot urine collection. However, more research is required into threshold selection for children and this requires prospective data tying urine ACR to future clinical events.

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DATA SHARING STATEMENT: Dataset and technical documents are available from *Growing Up in Australia*: The Longitudinal Study of Australian Children via low-cost license for bone fide researchers. More information is available at www.growingupinaustralia.gov.au

FIGURE CAPTIONS AND FOOTNOTES:

Figure 1: Participant flow chart

n=number of families, c=number of children, p=number of attending adults, MAC=Main assessment centre, mAC=Mini assessment centre, HV=Home visit assessment, LSAC=Longitudinal Study of Australia Children.

*Unable to analyse due to insufficient volume of poor quality sample

^Data excluded from 2 children and 1 parent with ACR>200mg/mmol or Albumin>2000mg/L, and data from 15 non-biological child-parent pairs excluded from concordance analyses.

Figure 2: Density plots for urine measures

— Girls/Mothers; — Boys/Fathers; - - - All.

mg: milligrams; mmol: millimoles; L: litres.

Graphs plot log-transformed data, with x-axes labelled using actual values for ease of interpretation.

Figure 3: Parent-child pair scatter plots

mg: milligrams; mmol: millimoles; L: litres.

Graphs plot log-transformed data, with x-axes labelled using actual values for ease of interpretation.

SUPPLEMENTARY DOCUMENT DESCRIPTIONS: supplementary appendix containing

Supplementary table S1: Further measures describing the distribution of the data

Supplementary table S2a: Percentile data for urine measures by sex

Supplementary table S2b: Percentile data for urine measures overall for each age cohort

Supplementary table S3a: Mother-child concordance

Supplementary table S3b: Father-child concordance

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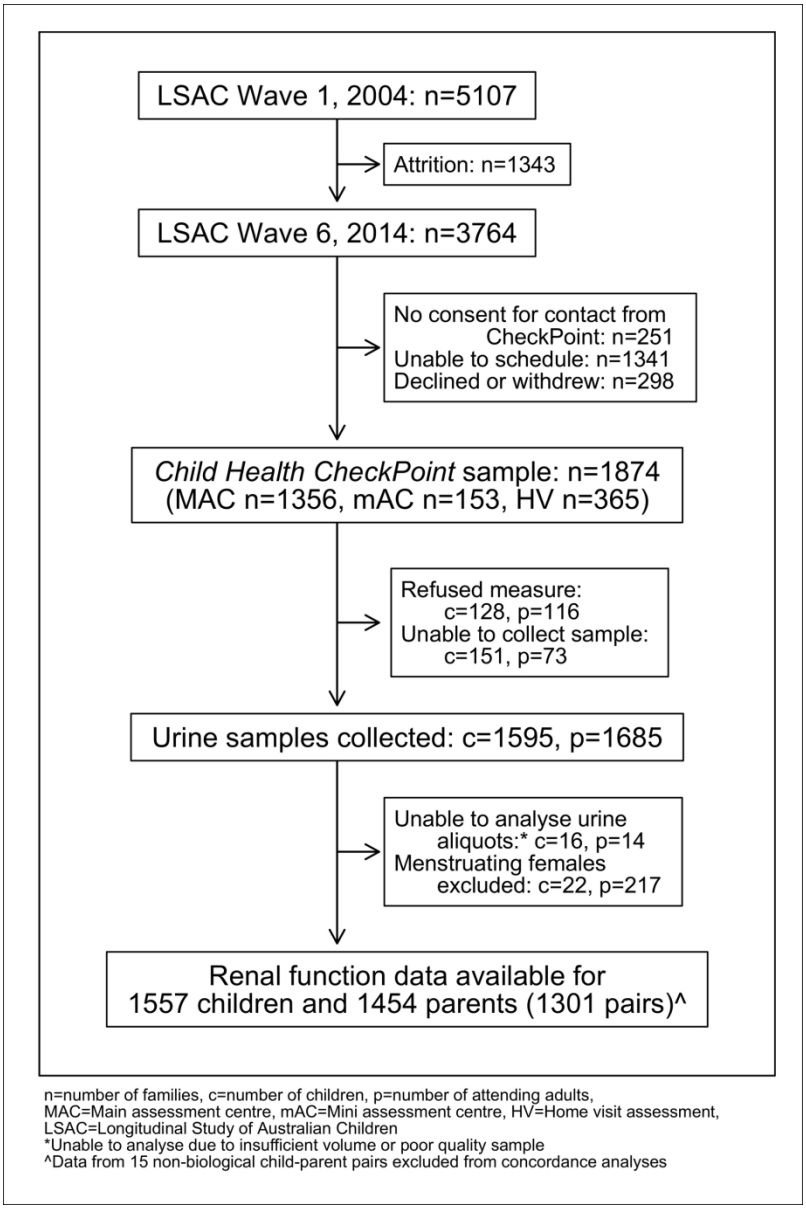

Figure 1: Participant flow chart
n=number of families, c=number of children, p=number of attending adults, MAC=Main assessment centre, mAC=Mini assessment centre, HV=Home visit assessment, LSAC=Longitudinal Study of Australia Children.
*Unable to analyse due to insufficient volume of poor quality sample
^Data excluded from 2 children and 1 parent with ACR>200mg/mmol or Albumin>2000mg/L, and data from 15 non-biological child-parent pairs excluded from concordance analyses.

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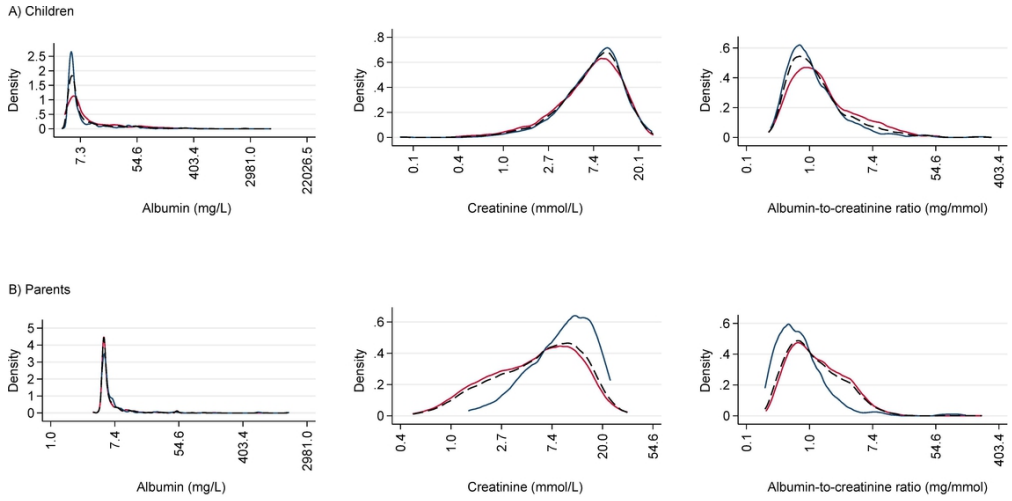

Figure 2: Density plots for urine measures
Red line: Girls/Mothers; Blue line: Boys/Fathers; Black, dotted line: All.
mg: milligrams; mmol: millimoles; L: litres.
Graphs plot log-transformed data, with x-axes labelled using actual values for ease of interpretation.

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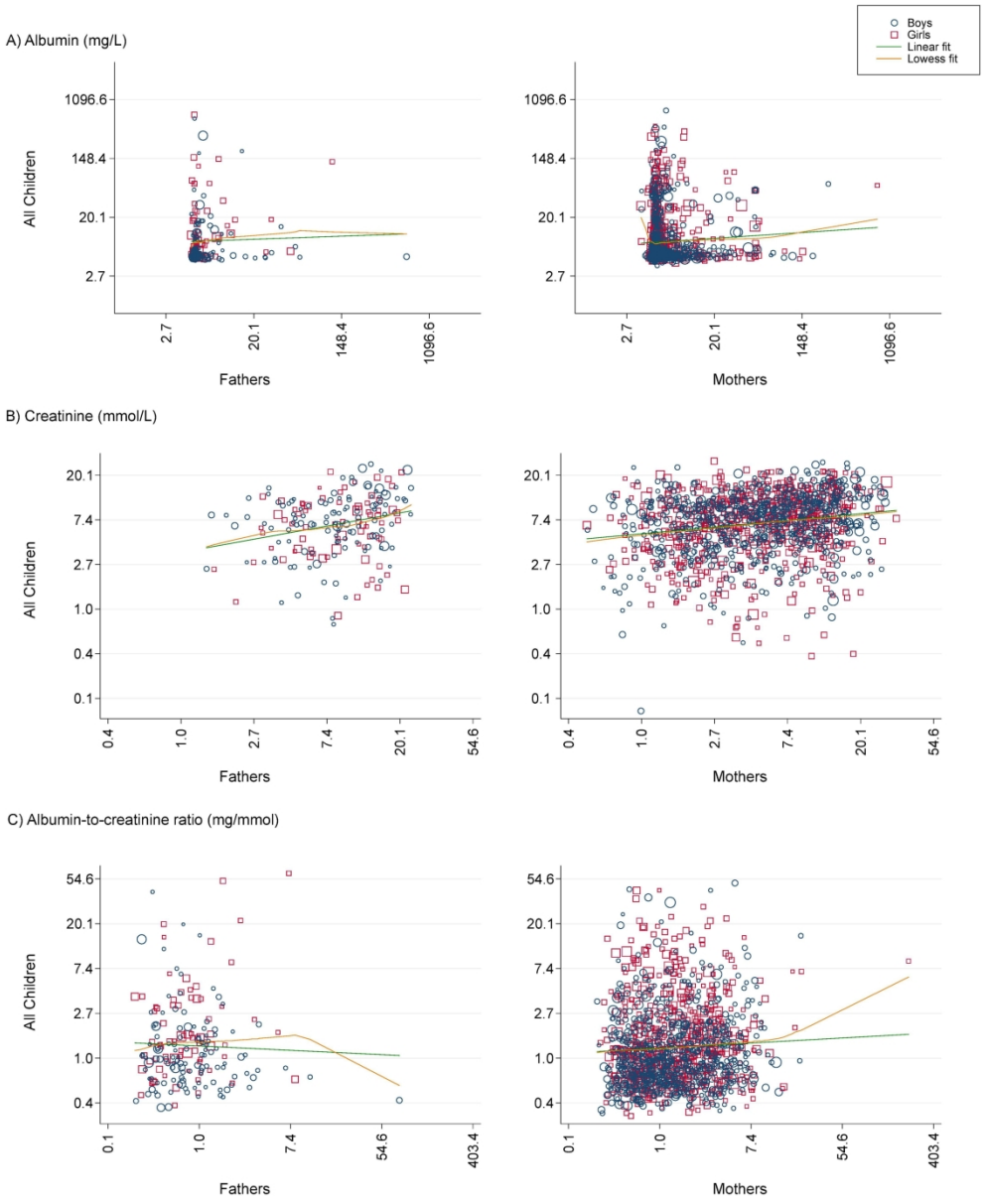

Figure 3: Parent-child pair scatter plots
mg: milligrams; mmol: millimoles; L: litres.
Graphs plot log-transformed data, with x-axes labelled using actual values for ease of interpretation.

221x270mm (300 x 300 DPI)

Supplementary table S1. Further measures describing the distribution of the data*

Variable	Male				Female			
	N	Mean	SD	95% CI	N	Mean	SD	95% CI
Children								
Albumin (mg/L)	837	24.6	182.0	11.1 to 38.1	720	21.8	50.4	17.2 to 26.0
Creatinine (mmol/L)	837	8.7	4.8	8.3 to 9.1	720	8.4	4.9	7.8 to 8.7
Albumin creatinine ratio	837	2.6	12.8	1.5 to 3.7	720	3.0	5.8	2.5 to 3.5
Ln albumin (ln (mg/L))	837	2.1	0.9	2.0 to 2.2	720	2.4	1.0	2.2 to 2.4
Ln Creatinine (ln (mmol/L))	837	2.0	0.7	1.9 to 2.0	720	1.9	0.7	1.8 to 2.0
Ln albumin creatinine ratio	837	0.1	0.9	0.0 to 0.2	720	0.4	1.0	0.3 to 0.5
Adults								
Albumin (mg/L)	211	18.4	118.2	3.3 to 33.5	1243	8.9	21.5	7.5 to 9.9
Creatinine (mmol/L)	211	10.6	5.6	9.6 to 11.6	1243	7.1	5.5	6.8 to 7.6
Albumin creatinine ratio	211	2.0	10.9	0.6 to 3.5	1243	2.0	5.2	1.7 to 2.2
Ln albumin (ln (mg/L))	211	1.9	0.7	1.8 to 2.0	1243	1.8	0.5	1.8 to 1.9
Ln Creatinine (ln (mmol/L))	211	2.2	0.6	2.1 to 2.3	1243	1.6	0.9	1.6 to 1.7
Ln albumin creatinine ratio	211	-0.3	0.9	-0.1 to -0.4	1243	0.2	0.9	0.2 to 0.3

SD: standard deviation; CI: confidence interval; Ln: natural logarithm. * Data present a right skewed distribution.

Supplementary tables S2a. Percentile data for urine measures by sex

	Male							Female						
Variable	**P5**	**P10**	**P25**	**P50**	**P75**	**P90**	**P95**	**P5**	**P10**	**P25**	**P50**	**P75**	**P90**	**P95**
Children														
Albumin (mg/L)	4.94	5.04	5.26	5.63	7.62	25.98	51.11	5.04	5.16	5.42	6.74	13.18	50.76	88.45
Creatinine (mmol/L)	2.07	2.99	5.00	8.03	11.31	15.09	17.84	1.56	2.59	4.49	7.65	11.33	15.05	17.27
Albumin creatinine ratio	0.42	0.47	0.61	0.90	1.65	3.55	6.03	0.45	0.52	0.74	1.20	2.65	6.93	10.82
Adults														
Albumin (mg/L)	4.97	5.06	5.22	5.50	6.60	9.13	20.73	4.91	5.01	5.18	5.42	6.38	10.57	17.24
Creatinine (mmol/L)	2.72	3.78	5.95	9.65	14.82	19.05	20.50	1.10	1.48	2.66	5.88	10.34	14.56	17.51
Albumin creatinine ratio	0.29	0.34	0.41	0.66	1.05	1.96	3.28	0.39	0.46	0.69	1.13	2.33	4.22	5.78

Supplementary tables S2b. Percentile data for urine measures overall for each age cohort

Variable	**P5**	**P10**	**P25**	**P50**	**P75**	**P90**	**P95**
Children							
Albumin (mg/L)	4.96	5.09	5.31	5.91	9.83	33.66	68.69
Creatinine (mmol/L)	1.79	2.76	4.74	7.88	11.32	15.05	17.32
Albumin creatinine ratio	0.43	0.48	0.65	1.03	1.97	4.82	8.96
Adults							
Albumin (mg/L)	4.92	5.02	5.19	5.43	6.43	10.51	17.24
Creatinine (mmol/L)	1.16	1.59	3.00	6.41	11.16	15.31	18.60
Albumin creatinine ratio	0.37	0.42	0.60	1.01	2.09	4.02	5.40

Supplementary table S3a. Mother-child concordance

Variable	Male			Female		
Pearson's Correlation	**N**	**CC**	**95% CI**	**N**	**CC**	**95% CI**
Albumin (mg/L)	588	0.04	-0.05 to 0.12	523	0.03	-0.01 to 0.16
Creatinine (mmol/L)	589	0.23	0.15 to 0.30	523	0.15	0.07 to 0.24
Albumin creatinine ratio	588	0.09	0.01 to 0.17	523	0.03	0.00 to 0.17
Multivariable Linear Regression*	**N**	**RC**	**P-value**	**N**	**CC**	**95% CI**
Albumin (mg/L)	586	0.03	0.7	520	0.11	0.1
Creatinine (mmol/L)	587	0.17	<0.001	520	0.11	0.002
Albumin creatinine ratio	586	0.10	0.01	520	0.03	0.09
Partial correlation coefficient*	**N**	**RC**		**N**	**CC**	
Albumin (mg/L)	586	0.02		520	0.03	
Creatinine (mmol/L)	587	0.21		520	0.1	
Albumin creatinine ratio	586	0.10		520	0.07	

CC: correlation coefficient; RC: estimated regression coefficient; CI: confidence interval

* Adjusted for parent age, Index of Relative Socioeconomic Disadvantage, child and parent body mass index, parent and child sex. Albumin, creatinine and albumin creatinine ratio have been log transformed.

Supplementary table S3b. Father-child concordance

Variable	Boys			Girls		
Pearson's Correlation	**N**	**CC**	**95% CI**	**N**	**CC**	**95% CI**
Albumin (mg/L)	117	0.00	-0.18 to 0.18	72	0.21	-0.04 to 0.41
Creatinine (mmol/L)	117	0.26	0.08 to 0.42	72	0.11	-0.11 to 0.35
Albumin creatinine ratio	117	-0.16	-0.33 to 0.03	72	0.27	0.03 to 0.46
Multivariable Linear Regression*	**N**	**RC**	**P-value**	**N**	**CC**	**95% CI**
Albumin (mg/L)	114	0.05	0.7	72	0.42	0.07
Creatinine (mmol/L)	114	0.31	0.004	72	0.18	0.3
Albumin creatinine ratio	114	-0.18	0.08	72	0.39	0.03
Partial correlation coefficient*	**N**	**RC**		**N**	**CC**	
Albumin (mg/L)	114	0.04		72	0.22	
Creatinine (mmol/L)	114	0.28		72	0.14	
Albumin creatinine ratio	114	-0.17		72	0.27	

CC: correlation coefficient; RC: estimated regression coefficient; CI: confidence interval.

* Adjusted for parent age, Index of Relative Socioeconomic Disadvantage, child and parent body mass index, parent and child sex. Albumin, creatinine and albumin creatinine ratio have been log transformed.

STROBE Statement—checklist of items that should be included in reports of observational studies

Paper title: Albuminuria: Population epidemiology and concordance in 11-12 year old Australians and their parents

Person completing checklist: Nicholas Larkins

	Item No	Recommendation	Page number
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up ~~*Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale~~ for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5
		~~(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed~~ ~~*Case-control study*—For matched studies, give matching criteria and the number of controls per case~~	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6, 7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6, 7
Bias	9	Describe any efforts to address potential sources of bias	6, 7
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6, 7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	7
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed ~~*Case-control study*—If applicable, explain how matching of cases and controls was addressed~~ ~~*Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy~~	NA
		(*e*) Describe any sensitivity analyses	NA

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	Figure 1
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10
		(b) Indicate number of participants with missing data for each variable of interest	Table 2
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	NA
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	12
		Cross-sectional study—Report numbers of outcome events or summary measures	12
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	12
		(*b*) Report category boundaries when continuous variables were categorized	6 Table 2
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15, 16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	16
Generalisability	21	Discuss the generalisability (external validity) of the study results	16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.