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ALBUMINURIA AND INCIDENT CORONARY HEART DISEASE IN AUSTRALIAN ABORIGINAL PEOPLE

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Abstract

Background. It has been suggested that albuminuria is useful in identifying persons at increased risk of coronary heart disease (CHD). Australian Aborigines have exceedingly high rates of renal failure together with increased CHD mortality. We undertook this prospective cohort study to assess the independent effect of albuminuria on CHD risk in Aboriginal people in the Northern Territory of Australia.

Methods. We examined the relation between micro- and macroalbuminuria and incident CHD in a sample of 870 Aboriginal adults aged 20 to74 years old without prevalent baseline CHD. Cox proportional hazards models were used to assess the association between baseline albuminuria and CHD incidence.

Results. During a median of 9.2 years of follow-up, 89 CHD events occurred during the follow-up period (1992 to 2003). The incidence of CHD increased significantly across categories of albuminuria (4.4, 10.9, and 29.8 per 1000 person-years for normoalbuminuria, microalbuminuria, and macroalbuminuria, respectively). The multiple Cox proportional hazards regression showed the hazard ratio was 3.4 (95% CI 1.6, 7.3), adjusting for age, gender, body mass index (BMI), blood pressure, total cholesterol, diabetes status, cigarette smoking, and alcohol consumption, for macroalbuminuria group. Hazard ratio for microalbuminuria group was not significantly different from unity during the first 6 years of follow-up but significantly higher during the follow-up period >6 years with adjusted hazard ratio 9.0 (95% CI 2.0, 40.0).

Conclusion. Independent of traditional cardiovascular risk factors, both microalbuminuria and macroalbuminuria may be useful in identifying persons at increased risk of CHD in Aboriginal people.

Keywords: albuminuria, coronary disease, prospective studies, risk factors, Aborigines.

Aboriginal Australians have a high rate of end-stage of renal disease (ESRD) together with increased cardio-vascular mortality [1]. They also have higher prevalence of albuminuria than Australians of European descent [2]. An association between albuminuria and subsequent cardiovascular mortality in Aboriginal people was demonstrated [3]. Cross-sectional studies showed a powerful association between albuminuria and cardiovascular risk factors [4–6]. It has been found in non-Aboriginal populations that any degree of albuminuria is a risk factor for cardiovascular events in diabetic and nondiabetic individuals [7]. Microalbuminuria is useful in identifying persons at increased risk of coronary heart disease (CHD) in the general British population [8].

Although the significance of albuminuria as a possible predictor of CHD has been suggested [6, 9], there has not been a cohort study of albuminuria and incident CHD in Aboriginal people. It is not clear if the association between albuminuria and CHD risk is independent of the traditional risk factors this population. Therefore, we undertook this prospective study, with a median of 9.2 years of follow-up, to examine the relationship between albuminuria levels and future CHD events.

METHODS

From 1992 to 1995, a community-wide renal disease screening program, involving 897 adults aged 20 to 74 years old, was conducted in a remote island community in Northern Territory. There were 878 who had a baseline measurement of urine albumin/creatinine ratio. Eight participants were excluded because their hospital records showed preexisting CHD events. Thus, 870 people representing over 80% the adult population in the community were included in this study.

Measurements

The urinary albumin and creatinine concentrations were measured on a random urine specimen. Urinary albumin concentration was measured by the Beckman immunoassay (Beckman Instruments, Fullerton, CA, USA). An albumin:creatinine ratio (ACR) was calculated (mg/mmol). Previous studies in Aboriginal people used 3.4 mg/mmol and 34 mg/mmol as cutoffs for micro-and macro- (or overt) albuminuria [3–6].

Other studies defined microalbuminuria as an ACR of 2.0 mg/mmol [7]. However, to be consistent with recent cohort studies on predictive values of albuminuria on heart disease, this study defined normoalbuminuria as an ACR less than 2.5 mg/mmol, microalbuminuria as an ACR 2.5 to 25 mg/mmol, and macroalbuminuria as an ACR greater than 25 mg/mmol [8, 10, 11]. CHD risk factors such as blood pressures, serum cholesterol, triglycerides, body mass index (BMI), cigarette smoking, alcohol drinking, and the presence of diabetes were described elsewhere [12–14].

CHD

We identified fatal and nonfatal CHD events occurring between baseline and follow-up through December 31, 2003. CHD events were defined from hospital and death records using the codes of *Internationl Classification of Diseases, Ninth edition* (ICD-9-CM) codes 410–414 and ICD-10-AM codes I20-I25. Hospital Registration Numbers were used to link CHD events with baseline data.

Table 1. Baseline characteristics of study participants by categories of albuminuria

	Albumin:creatinine ratio (ACR) category			
	Normoalbuminuria	Microalbuminuria	Macroalbuminuria	
	0.00–2.49 mg/mmol	2.50–25.0 mg/mmol	>25 mg/mmol	*P* value
Number (%)	389 (45)	265 (30)	216 (25)	
Age *years*	30.3 (10.2)	34.5 (11.8)	41.6 (12.3)	<0.001
Body mass index *kg/m2*[a]	22.3 (4.7)	24.4 (5.2)	26.1 (5.7)	<0.001
Total cholesterol *mmol/L*[a]	4.4 (1.0)	4.7 (1.0)	5.2 (1.3)	<0.001
Systolic pressure *mm Hg*[a]	116.5 (16.4)	122.0 (16.5)	130.5 (20.8)	<0.001
Diastolic pressure *mm Hg*[a]	70.5 (11.4)	75.2 (13.2)	81.6 (15.2)	<0.001
UrineACR *mg/mmol*[b]	0.7 (0.7, 0.8)	7.3 (6.7, 7.9)	84.1 (75.8, 93.3)	<0.001
Triglycerides *mmol/L*[b]	1.6 (1.5,1.7)	1.9 (1.8, 2.0)	2.5 (2.3, 2.8)	<0.001
Male (%)	209 (53.7)	142 (53.6)	91 (42.1)	0.0132
Smoking (%)	294 (75.6)	186 (70.2)	148 (68.5)	0.1223
Drinking (%)	225 (57.8)	157 (59.2)	109 (50.5)	0.1166
Diabetes (%)	20 (5.1)	27 (10.2)	71 (32.9)	<0.001

[a] Mean (SD).
[b] Geometric mean (95% CI).

Statistical analysis

CHD incidence rates were calculated by dividing the number of first-ever CHD events by the person-years of follow-up according to the three categories of albuminuria. Hazard ratios and their 95% CIs were estimated using the Cox proportional hazards model, adjusting for potential confounding factors of *(1)* age and gender and *(2)* age, gender, smoking, alcohol drinking, blood pressure, BMI, serum cholesterol, and diabetes status.

Table 2. Pearson correlation coefficients between baseline albumin:creatinine ratio (ACR) and follow-up ACRs

Time after baseline	Correlation coefficients	Number
ACR year 1	0.8278	306
ACR year 2	0.7959	220
ACR year 3	0.7631	280
ACR year 4	0.7392	213
ACR year 5+	0.6412	146

In a subset of study sample, 598 participants had at least one subsequent urine ACR measurements from 1 to 5 years after the initial measurement. To understand how well the baseline ACR measurement

can reflect the usual ACR level during the follow-up period, correlation coefficients between initial measurement and subsequent measurements were calculated. All analyses were performed using Stata version 8 [15].

Ethics approval

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

RESULTS

Baseline characteristics

Thirty percent of participants had microalbuminuria and 25% had macroalbuminuria. Table 1 shows baseline characteristics of the study population by categories of albuminuria. Albuminuria was significantly associated with a number of cardiovascular risk factors, including age, blood pressure, total cholesterol, BMI, triglycerides, and diabetes.

Correlations between baseline and subsequent measurements

Based on a convenient sample, the baseline ACR measurement was significantly correlated with follow-up ACR measurements. The correlation decreased with the duration of follow-up from 0.83 at year 1 to 0.64 at year 5 after the baseline measurement (Table 2).

Table 3. Incidence of coronary heart disease (CHD) by categories of albuminuria in Aboriginal people

Albuminuria	CHD events	Person-years	Incidence (95% CI)/ 1000 person-years
Normal	15	3426.7	4.4 (2.6, 7.3)
Micro	25	2297.6	10.9 (7.4, 16.1)
Macro	49	1645.1	30.0 (22.5, 39.4)

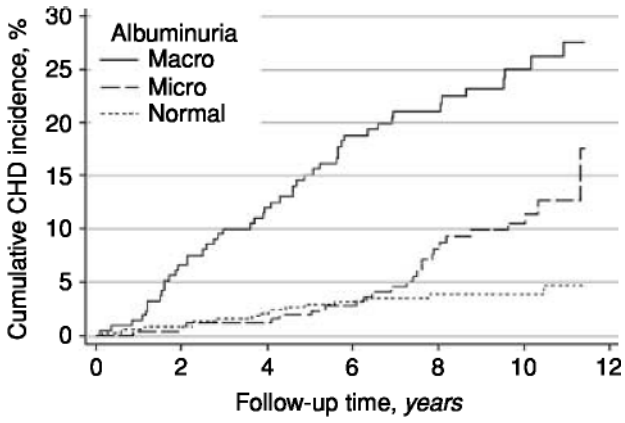

Fig. 1. Albuminuria and coronary heart disease (CHD) incidence in Aboriginal Australians.

Association between albuminuria and CHD

A total of 89 CHD events occurred during a median of 9.2 years in 870 participants. Fifty one (57%) participants had acute myocardial infarction and 26 (29%) had angina pectoris. As is shown in Table 3 and Figure 1, the incidence of CHD increased significantly across categories of base-line albuminuria. After adjusting for age and gender with normoalbuminuria as the reference group, the CHD risk was about doubled for microalbuminuria and about four-fold for macroalbuminuria during the whole follow-up period (Table 4). The increased CHD risk for microalbuminuria and macroalbuminuria groups remained after adjustment for major CHD risk factors including age, gender, BMI, blood pressure, total cholesterol, diabetes status, cigarette smoking, and alcohol consumption. The risk of CHD for

microalbuminuria group increased dramatically after 6 years. We divided the follow-up time into two periods: <6 years and >_6 years. The interaction term between follow-up time and microalbuminuria was found to be statistically significant. Therefore, the hazard ratios for two time periods are presented in Table 4. The hazard ratio 0.96 (0.34, 2.7) for microalbuminuria group was not significantly different from unity during early follow-up period although it was significantly higher during the period >6 years (Table 4).

Table 4. Hazard ratios (95% CI) for coronary heart disease (CHD) by categories of albuminuria in Aboriginal people

	Overall follow-up period		Follow-up time <6 years		Follow-up time ≥6 years	
Albuminuria	HR[a]	HR[b]	HR[a]	HR[b]	HR[a]	HR[b]
Normal	1	1	1	1	1	1
Micro	2.0 (1.04, 3.8)	2.6 (1.2, 5.5)	0.68 (0.27, 1.7)	0.96 (0.34 2.7)	7.3 (2.1, 25.2)	9.0 (2.0, 40.0)
Macro	3.9 (2.1, 7.2)	3.4 (1.6, 7.3)	3.5 (1.8, 7.0)	2.9 (1.2, 7.0)	5.1 (1.4, 18.8)	4.9 (1.0, 24.8)

Body mass index, blood pressure, and total cholesterol were continuous variables. Diabetes status, cigarette smoking and alcohol consumption were dichotomous.

[a] Adjusting for age and gender.

[b] Adjusting for age, gender, body mass index, blood pressure, total cholesterol, diabetes status, cigarette smoking, and alcohol consumption.

DISCUSSION

A growing number of epidemiologic studies have re-ported that microalbuminuria is a strong risk factor ofcardiovascular disease [7, 8, 16–20]. This study confirmed that the incidence of CHD increased significantly across categories of baseline albuminuria in Aboriginal people. Microalbuminuria and macroalbuminuria were in-dependently associated with an increased risk of CHD in comparison with normoalbuminuria. Therefore, microalbuminuria and macroabuminuria may be useful indicators, in addition to conventional risk factors such as age gender, smoking, total cholesterol, blood pressure, BMI, and diabetes, in identifying persons who are at increased risk of primary CHD.

The data are consistent with previous studies in Aboriginal populations which showed albuminuria associated with cardiovascular risk factors [4, 5, 12, 21]. Our prospective data indicate that the contribution of albuminuria to CHD risk is independent of traditional risk factors. Microalbuminuria was found to be an independent predictor of CHD risk in the general British population in the EPIC-Norfolk Study [8], and in a sample from North America, South America and Europe in the Heart Out-comes Prevention Evaluation (HOPE) study [7].

Our study participants had a higher prevalence of albuminuria than other published data. We found 30% microalbuminuria and 25% macroalbuminuria in our study sample while in the British population there are only 11.6% microalbuminuria and 0.8% macroalbuminuria [8]. An Australian study has shown that Aboriginal Australians have a higher prevalence of albuminuria than Australians of European decent [2]. However, the association between albuminuria and CHD risk in Aboriginal people in this study is consistent with findings in other populations. The age- and gender-adjusted hazard ratio for CHD associated with microalbuminuria for the over-all follow-up period is 1.98 (95% CI 1.04, 3.79) in our study while the corresponding ratio is 1.65 for British population [8]. The hazards ratio for major cardiovascular events associated with microalbuminuria in the HOPE study is 1.83 [7]. Although similar relative risks have been found across different populations, microalbuminuria may play a more important role in Aboriginal population due to its higher prevalence of microalbuminuria.

Some limitations of this study should be pointed out. First, the CHD events were identified through hospital inpatient and death records. Some minor CHD events not severe enough for hospitalization may have been missed. Second, the risk of albuminuria measured on a single occasion at baseline tends to underestimate the true association between “usual” albuminuria level and CHD. Regression dilution bias is one of concerns for using baseline risk values in cohort studies with a long period of follow-up [22–24]. The magnitude of regression dilution increases with increasing length of follow-up [24]. The correlation coefficients between baseline measurement and resurveyed values have been used to assess the magnitude of the bias [24]. The correlation coefficient

for ACR between baseline and year 5 (r = 0.64) is similar to those for systolic and diastolic blood pressures in Framingham and MONICA data [24]. Therefore, the presence of dilution bias tends to underestimate the true association between albuminuria and CHD risk. Third, a subset of study participants with ACR >34 g/mol or diabetes and ACR >3.4 g/mol received an angiotensinconverting

enzyme (ACE) inhibitor (perindopril) treatment during the follow-up period. [25] Due to the beneficial effects of ACE inhibitor and the fact that the treatment mostly occurred in albuminuria groups,[25] the incidence of CHD could have been higher in albuminuria groups if the treatment had not been used in this population. Therefore, the use of ACE inhibitors among study participants might have diluted the true association between albuminuria and CHD. Fourth, although the microalbuminuria group had an increased CHD incidence than the normal group during the overall follow-up period, the significant difference only appeared after 6 years of follow-up. It remains unanswered if the progression from micro- to macroalbuminuria during the follow-up period contributed to this pattern.

The underlying pathophysiologic mechanism behind the association between albuminuria and CHD is still not clear. There are several possible explanations. Albuminuria is a marker of established CHD risk factors. There is a large body of data demonstrating associations between microalbuminuria and established cardiovascular risk factors, including elevated blood pressure, elevated lipid levels, adiposity, carotid intima-media thickness, smoking, and diabetes in both Aboriginal and other populations [4, 5, 12, 21]. In the present study we observed an association between albuminuria and major risk factors such as total cholesterol, blood pressure, and diabetes. However, the association may not be mediated by those factors since the association remained after adjustment of those factors. It is suggested that albuminuria may reflect endothelial dysfunction that might enhance the penetration of atherogenic lipoproteins into the arterial wall [26]. The study of Jensen [27] indicates that atherosclerotic vascular disease is associated with renal and systemic transvascular leakiness for albumin, and such leakiness may allow for an increased lipid insudation into the large vessel wall, thereby linking microalbumin-uria to atherogenesis. However, Agewall and Bjorn [28] suggested microalbuminuria in healthy subjects is not primarily associated with atherosclerosis but rather to blood pressure and abdominal obesity.

Although the true explanation of the pathophysiologic relationship between albuminuria and CHD is still not clear, it is important to know that microalbuminuria is a useful independent predictor of CHD risk. Improving kidney function may be potentially beneficial to preventing CHD in Aboriginal people. Our results suggest that microalbuminuria and macroalbuminuria can be useful for identifying persons at increased risk of CHD who might benefit the most from treatment. Conventional risk factors underestimated the risk of CHD in Aboriginal people [29]. Albuminuria may be a useful indicator in the absolute risk equations in addition to conventional risk factors.

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REFERENCES

1. AUSTRALIAN INSTITUTE OF HEALTH AND WELFARE (AIHW): *Heart, stroke and vascular diseases—Australian facts 2004,* Canberra, AIHW and National Heart Foundation of Australia (Cardiovascular Disease Series No. 22), 2004
2. GUEST CS, RATNAIKE S, LARKINS RG: Albuminuria in Aborigines and Europids of South-Eastern Australia. *Med J Aust* 159:335–338, 1993
3. HOY WE, WANG Z, VANBUYNDER P, *et al:* The natural history of renal disease in Australian Aborigines. Part 2. Albuminuria predicts natural death and renal failure. *Kidney Int* 60:249–256, 2001
4. ROWLEY KG, ISER DM, BEST JD, *et al:* Albuminuria in Australian Aboriginal people: Prevalence and associations with components of the metabolic syndrome. *Diabetologia* 43:1397–1403, 2000
5. MCDONALD SP, MAGUIRE GP, HOY WE: Renal function and cardiovascular risk markers in a remote Australian Aboriginal community. *Nephrol Dial Transplant* 18:1555–1561, 2003
6. HOY W, MCDONALD SP: Albuminuria: Marker or target in indigenous populations. *Kidney Int* 66 (Suppl 92):S25–S31, 2004
7. GERSTEIN HC, MANN JF, YI Q, *et al:* Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. *JAMA* 286:421–426, 2001
8. YUYUN MF, KHAW KT, LUBEN R, *et al:* A prospective study of microalbuminuria and incident coronary heart disease and its prognostic significance in a British population: The EPIC-Norfolk study. *Am J Epidemiol* 159:284–293, 2004
9. HOY WE, MCFARLANE R, PUGSLEY DJ, *et al:* Markers for cardiovascular and renal morbidity: Expectations for an intervention pro-gramme in an Australian aboriginal community. *Clin Exp Pharmacol Physiol* 23:S33–S37, 1996

10. MOGENSEN CE: Microalbuminuria and hypertension with focus on type 1 and type 2 diabetes. *J Intern Med* 254:45–66, 2003

11. MOGENSEN CE, KEANE WF, BENNETT PH, *et al:* Prevention of diabetic renal disease with special reference to microalbuminuria. *Lancet* 346:1080–1084, 1995

12. HOY WE, WANG Z, VANBUYNDER P, *et al:* The natural history of renal disease in Australian Aborigines. Part 1. Changes in albuminuria and glomerular filtration rate over time. *Kidney Int* 60:243–248, 2001

13. WANG Z, HOY WE: Association between diabetes and coronary heart disease in Aboriginal people: Are women disadvantaged? *Med J Aust* 180:508–511, 2004

14. WANG Z, HOY WE: Waist circumference, body mass index, hip circumference and waist-to-hip ratio as predictors of cardiovascular disease in Aboriginal people. *Eur J Clin Nutr* 58:888–893, 2004

15. STATACORP: *Stata Statistical Software: Release 8.0,* College Station. TX, Stata Corporation, 2003

16. AGEWALL S, WIKSTRAND J, LJUNGMAN S, *et al:* Usefulness of microalbuminuria in predicting cardiovascular mortality in treated hypertensive men with and without diabetes mellitus. Risk Factor Intervention Study Group. *Am J Cardiol* 80:164–169, 1997

17. LJUNGMAN S, WIKSTRAND J, HARTFORD M, *et al:* Urinary albumin excretion—A predictor of risk of cardiovascular disease. A prospective 10-year follow-up of middle-aged nondiabetic normal and hypertensive men. *Am J Hypertens* 9:770–778, 1996

18. JAGER A, KOSTENSE PJ, RUHE HG, *et al:* Microalbuminuria and peripheral arterial disease are independent predictors of cardiovascular and all-cause mortality, especially among hypertensive subjects: Five-year follow-up of the Hoorn Study. *Arterioscler Thromb Vasc Biol* 19:617–624, 1999

19. YUYUN MF, KHAW KT, LUBEN R, *et al:* Microalbuminuria and stroke in a British population: The European Prospective Investigation into Cancer in Norfolk (EPIC-Norfolk) population study. *J Intern Med* 255:247–256, 2004

20. MATTOCK MB, BARNES DJ, VIBERTI G, *et al:* Microalbuminuria and coronary heart disease in NIDDM: An incidence study. *Diabetes* 47:1786–1792, 1998

21. MCDONALD SP, MAGUIRE GP, DUARTE N, *et al:* Carotid intimamedia thickness, cardiovascular risk factors and albuminuria in a remote Australian Aboriginal community. *Atherosclerosis* 177:423– 431, 2004

22. LEWINGTON S, THOMSEN T, DAVIDSEN M, *et al:* Regression dilution bias in blood total and high-density lipoprotein cholesterol and blood pressure in the Glostrup and Framingham prospective studies. *J Cardiovasc Risk* 10:143–148, 2003

23. MACMAHON S, PETO R, CUTLER J, *et al:* Blood pressure, stroke, and coronary heart disease. Part 1. Prolonged differences in blood pressure: Prospective observational studies corrected for the regression dilution bias. *Lancet* 335:765–774, 1990

24. CLARKE R, SHIPLEY M, LEWINGTON S, *et al:* Underestimation of risk associations due to regression dilution in long-term follow-up of prospective studies. *Am J Epidemiol* 150:341–353, 1999

25. HOY WE, BAKER PR, KELLY AM, *et al:* Reducing premature death and renal failure in Australian aboriginals. A community-based cardiovascular and renal protective program. *Med J Aust* 172:473–478, 2000

26. DECKERT T, FELDT-RASMUSSEN B, BORCH-JOHNSEN K, *et al:* Albuminuria reflects widespread vascular damage. The Steno hypothesis. *Diabetologia* 32:219–226, 1989

27. JENSEN JS: Renal and systemic transvascular albumin leakage in severe atherosclerosis. *Arterioscler Thromb Vasc Biol* 15:1324–1329, 1995

28. AGEWALL S, BJORN F: Microalbuminuria and intima-media thickness of the carotid artery in clinically healthy men. *Atherosclerosis* 164:161–166, 2002

29. WANG Z, HOY WE: Is the Framingham coronary heart disease absolute risk function applicable to Aboriginal people? *Med J Aust* 182:66–69, 2005