

RENAL DISEASE, THE METABOLIC SYNDROME, AND CARDIOVASCULAR DISEASE

Objectives: To describe the association between renal disease and other features of the metabolic syndrome and its derivative illnesses among Australian Aborigines in remote settings.

Methods: Volunteering adults ($N=2019$) in four remote communities were screened for risk factors and markers of renal disease, hypertension, and diabetes, and their cross-sectional associations were evaluated. Rates of the metabolic syndrome were estimated in one community with comprehensive screening data. The associations of albuminuria with hospitalizations, coronary heart events, and non-renal deaths were then followed for >7 years in that same community.

Results: Rates of renal disease, hypertension, and diabetes all increased dramatically with age. They all overlapped. Renal disease and hypertension were the most prominent and earliest features of the syndrome, while diabetes was a later, less common and more variable manifestation. All were strongly correlated with waist measurements, and high waist measurements more comprehensively characterized those with illnesses than did the more restrictive definitions of the metabolic syndrome. Albuminuria predicted non-renal hospitalizations, first time coronary heart disease events, and all-cause death.

Conclusion: Albuminuria/proteinuria is an early and dominant element of a symptom complex that is marked by higher waist measurements, and it strongly predicts all-cause and cardiovascular illnesses and deaths. This finding implies a common background of risk factors for renal disease, hypertension, diabetes, and cardiovascular risk. The findings support integrated, rather than disease-specific, surveillance programs, an important role for albuminuria in predicting non-renal risk, and a unified approach for primary and secondary prevention of all elements of the syndrome. (*Ethn Dis.* 2006;16[suppl 2]:S2-46–S2-51)

Key Words: Australian Aborigines, Metabolic Syndrome, Kidney Disease, Hypertension, Cardiovascular Disease, Diabetes Mellitus, Type 2 Diabetes

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INTRODUCTION

The metabolic syndrome might be considered an anthropomorphic and clinical profile that predisposes to cardiovascular risk. In the late 1980s and early 1990s, we and others proposed that renal disease might be, in part, a manifestation of the metabolic syndrome,^{1–3} on the grounds that epidemics of renal and cardiovascular disease are emerging simultaneously in many groups in health transition and that most people with end stage renal disease die of cardiovascular disease. In population studies, we and others showed that albuminuria correlates with many features of the metabolic syndrome⁴ and that albuminuria and decreased estimated glomerular filtration rate predict cardiovascular and other non-renal illness and deaths, as well as renal deaths.^{5–12}

Definitions of the metabolic syndrome are continuously developing. Among the current ones are the 1999 World Health Organization definition (WHO.MS), the Adult Treatment Panel (ATP) III (or National Cholesterol Education Program) definition (ATP.MS), and the 2005 International Diabetes Federation definition (IDF.MS) (Table 1).^{13–15} They can include three or more of various measures, including central obesity (variably defined), insulin resistance or dysglycemia or diabetes, higher cholesterol or triglycerides or

lower high-density lipoprotein levels, and various elevations of blood pressure. The WHO definition also includes pathologic albuminuria as an optional component of the metabolic syndrome and so already recognizes the links to renal disease. All definitions have the drawback of being dichotomous variables (yes or no), thus lacking any sensitivity to gradations of features, which is, of course, the pathophysiologic reality.

We describe cross-sectional data from remote Aboriginal communities in Australia's Northern Territory that support the concept that renal disease is a manifestation of the metabolic syndrome, and of the increased abdominal girth on which metabolic syndrome definitions, in part, depend. We also describe the powerful predictive value of albuminuria and proteinuria for cardiovascular as well as other, nonrenal illnesses and death on longitudinal study in one of these communities.

METHODS

Adult members (≥ 18 years) of communities 1, 2, and 3, whose data are presented in aggregate, were offered a brief health screening between 2000 and 2003, with 1070 people participating, or 70% of the adult population. The screening included a brief history, waist and hip, and blood pressure and blood glucose measurements. For this report, high blood pressure was defined by the IDF.MS definition of $\geq 130/85$ mm Hg. Urine was tested for protein by dipstick, with albumin-to-creatinine ratio (ACR) assayed if the dipstick was $\geq 1+$ or if the participant was hypertensive or diabetic. An aggregate diagnosis of renal disease was made if

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Table 1. Evolving definitions of the metabolic syndrome

<p><u>World Health Organization (WHO), 1999¹³</u> Impaired glycemic regulation or insulin resistance with at least two or more of the following: BMI > 30 or WHR > 0.9 in men or > 0.85 for women Blood pressure \geq 140/90 mmHg Microalbuminuria: Albumin excretion > 20 μg/min Triglycerides \geq 1.7 mmol/L or HDL < 0.9 mmol/L in men or < 1.0 mmol/L for women</p>
<p><u>National Cholesterol Education Program: Adult Treatment Panel (ATP) III, 2001¹⁴</u> Three or more of the following conditions: Waist circumference > 102 cm for men and > 88 cm for women Blood pressure \geq 135/85 mm Hg or on treatment for hypertension Fasting plasma glucose \geq 6.1 mmol/L Triglycerides \geq 1.7 mmol/L HDL < 1.0 mmol/L in men and < 1.3 mmol/L for women</p>
<p><u>International Diabetes Federation (IDF), 2005¹⁵</u> Ethnicity specific - waist circumference \geq 94 cm for Europid men and \geq 80 cm for Europid women with at least two or more of the following: Blood pressure \geq 130/85 mmHg or on treatment for hypertension Fasting plasma glucose \geq 5.6 mmol/L or known diabetes Serum triglycerides \geq 1.7 mmol/L or on treatment for dyslipidemia Serum HDL, <1.03 mmol/L in men and <1.29 mmol/L in women or on treatment for dyslipidemia</p>

a participant had proteinuria \geq 1+, an ACR 3.4+, and/or a past history of renal disease. Diabetes was defined by history, current hypoglycemic medicines, or levels of glycemia satisfying WHO criteria.

Nine hundred and thirty nine adults (\geq 18 years of age) in community 4, whose data are presented separately, were screened in the mid-1990s, with >90% of the adult population participating. Assessment included all the measures described above, but urine ACR and blood lipids were also measured in all participants. These enabled a more expansive and accurate diagnosis of renal disease, defined as urine ACR \geq 3.4 g/mol, as well as estimates of frequency of the metabolic syndrome.

Participants in the baseline screen in community 4 were then followed through the end of the 1999 for hospitalizations, until mid-2000 for deaths, and through the end of 2004 for first-time episodes of symptomatic coronary heart disease events, with the total period of follow-up as high as 7,369 years.

The associations of renal disease with hypertension, diabetes, and elevated waist measurements were evaluated on the community profiles on aggregated data

from communities 1, 2 and 3. The rates of the metabolic syndrome and their associations with renal disease were calculated in community 4. The predictive value of baseline levels of urine ACR for hospitalizations, first-time coronary heart disease events, and deaths were also evaluated in community 4.

RESULTS

Figure 1 shows a progressive increase of rates of renal disease, hypertension, and diabetes with age. In communities 1, 2, and 3, renal disease was less common than elevated blood pressure but both occurred at younger ages and with greater frequencies than diabetes. In community 4, which has higher rates of renal disease and in which ACR was the universal screening test, renal disease was the leading condition.^{16,17}

Extensive overlap of hypertension, renal disease, and diabetes is demonstrated by the Venn diagrams in Figures 2A and 2B. In communities 1, 2, and 3, renal disease was not often diagnosed in the absence of another

condition, but in community 4, the dominance of renal disease in the aggregated symptom complex is apparent. In both groups, people with diabetes nearly always had at least one co-existing condition.

Rates of overweight and obesity by body mass index criteria were not uniformly excessive relative to those in the Australian non-Aboriginal population^{18,19} but, waist measurements were often elevated, especially in females.¹⁷ All conditions were significantly correlated with waist measurements, as shown in Figures 3A and 3B. In multivariate modeling, waist, after age, was the most powerful correlate whose significance persisted after adjustment for all other factors (age, community, gender, alcohol use, smoking, and where available, birth weight).

Waist circumferences were elevated by IDF definitions in 72.9% of people in communities 1, 2, and 3, and in 48.3% of those in community 4. Rates of each disorder were significantly higher in people with high waist circumference, with rates increased 1.5- to 2-fold for hypertension, 2- to 2.5-fold for renal disease, and 3- to 4-fold for diabetes relative to those with normal waist circumference, after adjustment for age and sex (Table 2).

The proportions of people with the metabolic syndrome, which could only be calculated in community 4, were much lower than the proportions with elevated waist circumference. Table 3 shows that the (minimum) frequencies of the metabolic syndrome by the WHO, NCEP, and IDF definitions, respectively, were 22.2%, 25.9%, and 20.6%. No significant difference was seen by sex in those with WHO.MS, but more of those with ATP.MS and IDF.MS were female. This reflects the dominant role of elevated waist measurements, which are more common in females,¹⁷ in driving the latter two definitions. The IDF.MS definition was more completely embraced by the other definitions, with 88% of the

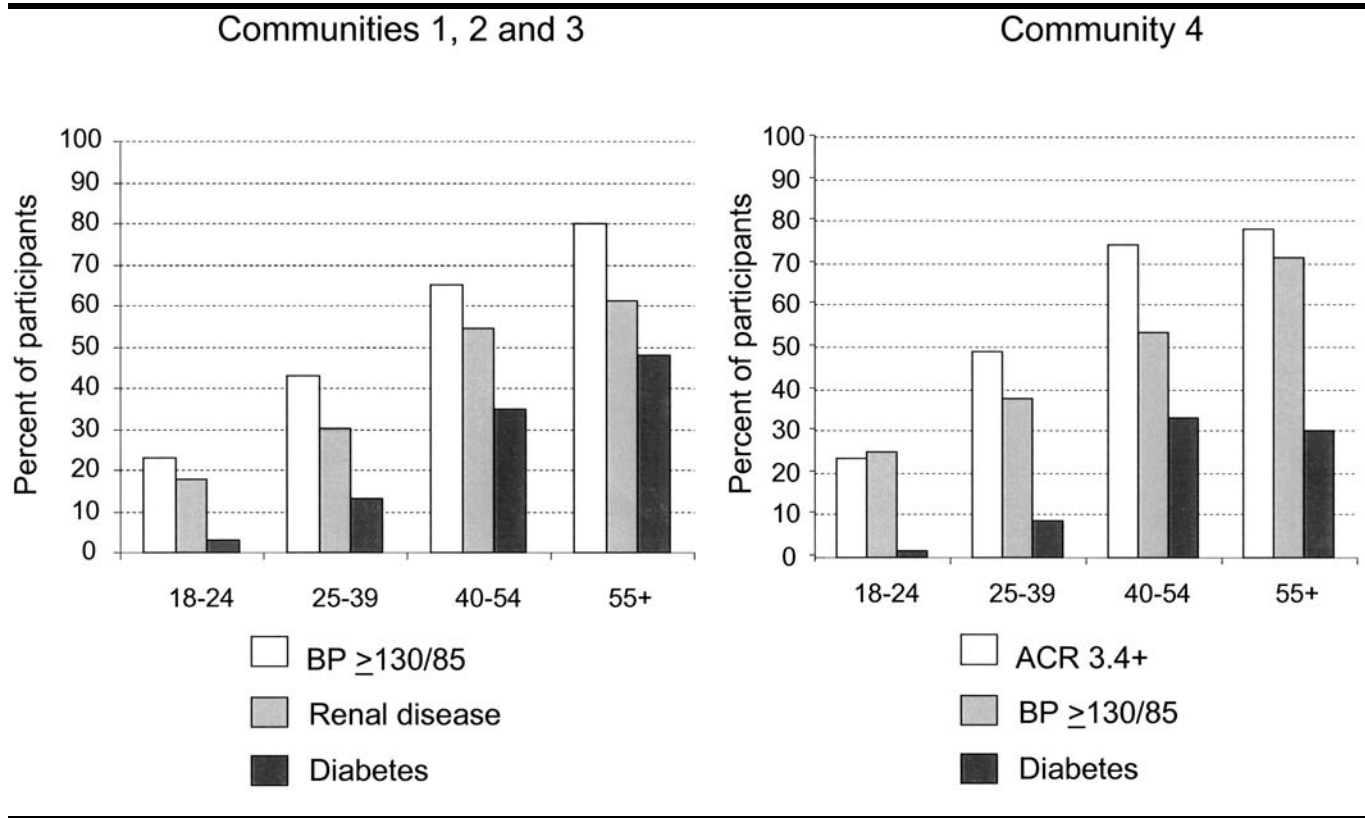


Fig 1. Prevalence of hypertension, renal disease and diabetes by age group

people so defined included in one or both of the other definitions (Figure 4). The table also shows considerable concentration of people with renal

disease among those with the metabolic syndrome, however renal disease was defined. This occurred to a similar extent in all definitions, although only

the WHO.MS has albuminuria as an optional defining criterion. However, 68.4% of people with renal disease did not qualify for a metabolic syndrome definition, a much larger proportion than the 36.1% who failed to qualify for a “high” waist measurement.

On longitudinal study in community 4, albuminuria at baseline powerfully predicted non-renal hospitalizations (Figure 5),²⁰ first time coronary heart disease events in previously unaffected people (Figure 6),¹¹ and all-cause death (Figure 7), as well as specifically cardiovascular death (Figure 8).^{8,9,21} Proteinuria similarly predicted these events, though with somewhat reduced discrimination.⁹

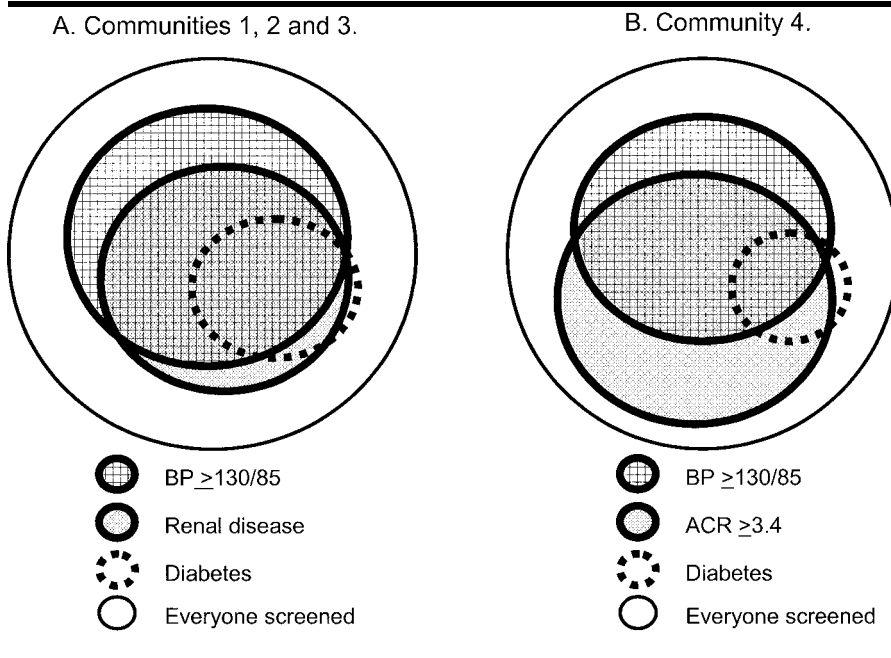


Fig 2. Overlap of hypertension, renal disease and diabetes

DISCUSSION

In these high-risk Aboriginal communities, increasing albuminuria or proteinuria, higher blood pressures and increasing levels of dysglycemia are all intimately

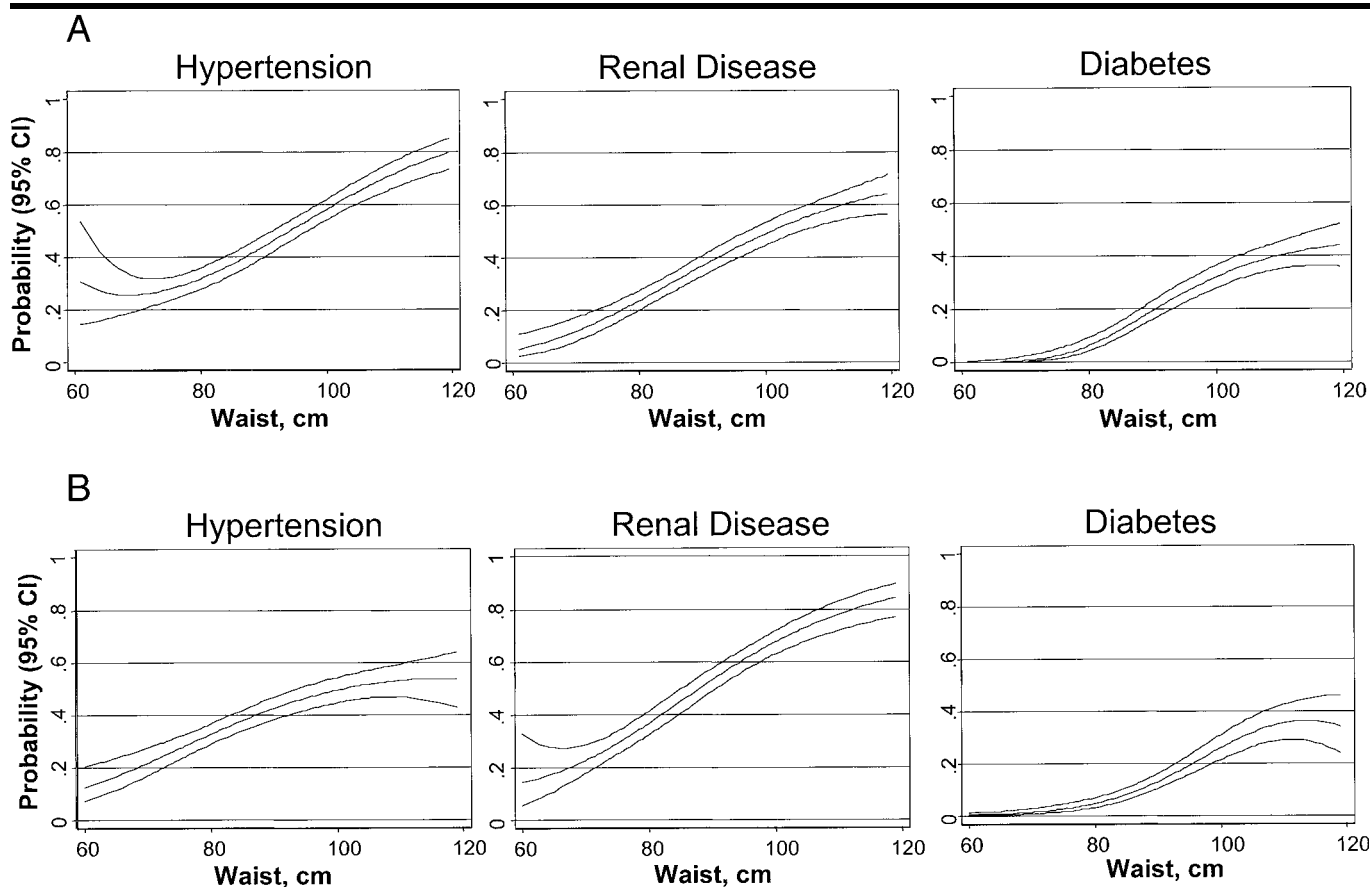


Fig 3A. Chronic disease and waist, communities 1, 2, and 3

Fig 3B. Chronic disease and waist, community 4

related. They are probably features of a single syndrome, of which albuminuria is an early and central manifestation. The co-existence of these conditions is compatible with the simultaneous epidemics of

cardiovascular disease, renal disease and diabetes in Aboriginal people. Albuminuria marks the risk for most of the morbid and fatal outcomes associated with these conditions.²²⁻²⁶

These conditions are more adequately marked by high waist measurements than by more restrictive definitions of the metabolic syndrome. The higher frequency of high waist measurements in females is compatible with their higher rates of renal disease and diabetes than males, at least through middle age.¹⁷

In multivariate modeling,⁵ central fat deposition, marked by waist circumference, is only one of several factors correlating with renal disease, but it is a very important one. Preferential central fat deposition, in turn, is itself a complex and multideterminant phenomenon, to which diet and exercise, prenatal and intrauterine conditions, inflammation, infections, alcohol, and arguably, genetics contribute.

A common background of risk factors^{5,27-29} implies that primary prevention relies on a common set of

Table 2. Prevalence of hypertension, renal disease and diabetes by categories of waist circumference, and odds ratios (95% confidence intervals), adjusted for age and sex

	BP \geq 130/ 85	OR (95% CI)	Renal Disease	OR (95% CI)	Diabetes	OR (95% CI)
Communities 1, 2, and 3						
High waist	53.1%	1.43 (1.06-1.94)	43.7%	2.16 (1.56-3.01)	26.0%	3.12 (1.93-5.05)
Normal waist	37.2%	Referent	22.1%	Referent	8.3%	Referent
Community 4						
High waist	56.4%	1.98 (1.4-2.8)	63.9%	2.48 (1.79-3.44)	22.2%	4.19 (2.45-7.14)
Normal waist	43.6%	Referent	33.2%	Referent	4.7%	Referent

P value for each set of observations <0.001.

Table 3. Prevalence of renal disease in community 4 and by metabolic syndrome definitions

	Dipstick $\geq 1+$	OR (CI)*	ACR 3.4+	OR (95% CI)	ACR 34+	OR (95% CI)
All adults	32.9%	Referent	48.4%	Referent	20.9%	Referent
WHO.MS	51.6%	2.93 (2.1-4.1)	76.9%	3.27 (2.2-4.8)	41.8%	2.76 (1.9-4.0)
NCEP.MS	56.7%	2.48 (1.8-3.4)	73.6%	2.73 (1.9-3.9)	43%	3.17 (2.2-4.5)
IDF.MS	51.9%	2.17 (1.5-3.1)	75.6%	2.82 (1.9-4.1)	42%	2.82 (1.1-4.1)

* OR (CI) adjusted for age and sex.

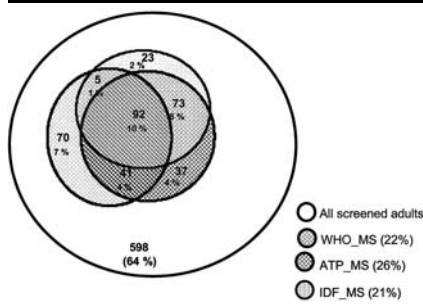


Fig 4. Metabolic syndrome by WHO, ATP, and IDF definitions in Aboriginal adults in community 4

strategies. The simultaneous expression dictates the need for integrated screening programs to detect early disease, and the late and more variable appearance of diabetes in the symptom complex shows that a diabetes-centric approach will be seriously deficient. Coexistence of illnesses implies that people will commonly need multidrug treatment,^{29,30} especially with advancing age, with antihypertensive, renal-sparing, hypoglycemic, lipid-lowering agents and aspirin and sometimes beta blockers often needed together. In that respect, particularly, a variety of fixed-dose

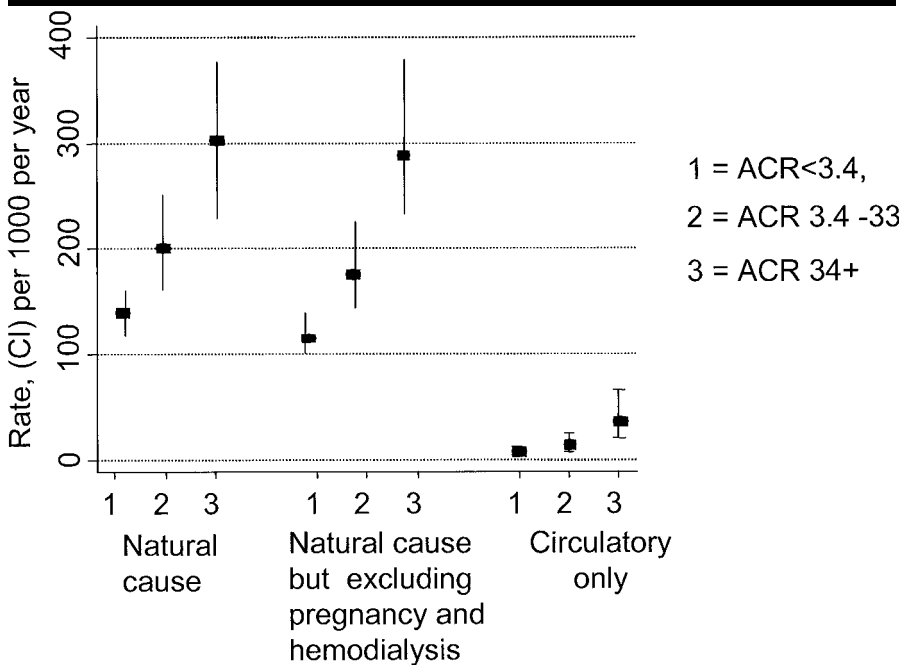


Fig 5. Hospitalizations in adults, in community 4 by baseline ACR category, adjusted for age and sex

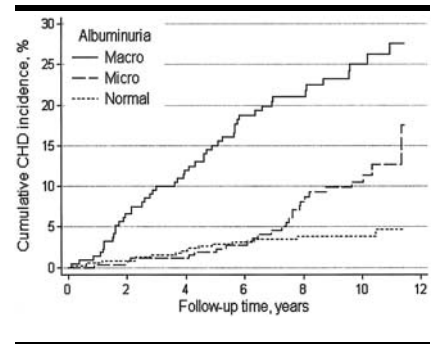


Fig 6. First coronary heart disease (CHD) events by baseline ACR category in community 4

combination medications³¹ and explorations of transdermal drug delivery systems would be of great benefit.

The integration of illnesses also means that healthcare providers and specialty groups must advocate with governments and other agencies with one voice for effective programs of primary and secondary prevention.³⁰ Much non-renal illness and premature death, as well as renal failure, will be avoided if this is done well.

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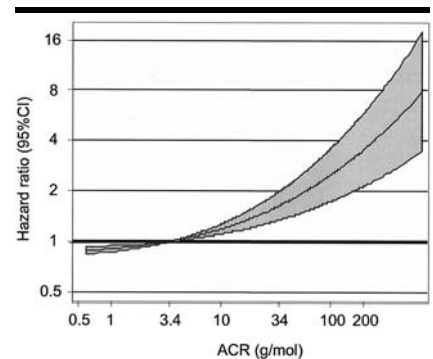


Fig 7. ACR-cause mortality risk by baseline ACR in community 4, adjusted for age and gender

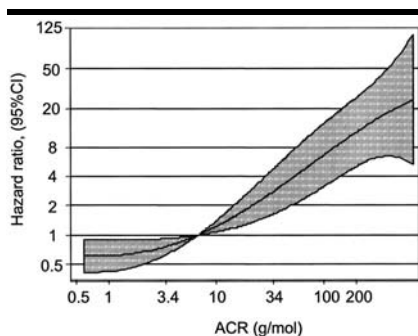


Fig 8. Cardiovascular mortality risk by baseline ACR in community 4

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Acquisition of funding: Hoy, Wang
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