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# Urinary Albumin Excretion Predicts Cardiovascular and Noncardiovascular Mortality in General Population

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**Background**—For the general population, the clinical relevance of an increased urinary albumin excretion rate is still debated. Therefore, we examined the relationship between urinary albumin excretion and all-cause mortality and mortality caused by cardiovascular (CV) disease and non-CV disease in the general population.

**Methods and Results**—In the period 1997 to 1998, all inhabitants of the city of Groningen, the Netherlands, aged between 28 and 75 years (n=85 421) were sent a postal questionnaire collecting information about risk factors for CV disease and CV morbidity and a vial to collect an early morning urine sample for measurement of urinary albumin concentration (UAC). The vital status of the cohort was subsequently obtained from the municipal register, and the cause of death was obtained from the Central Bureau of Statistics. Of these 85 421 subjects, 40 856 (47.8%) responded, and 40 548 could be included in the analysis. During a median follow-up period of 961 days (maximum 1139 days), 516 deaths with known cause were recorded. We found a positive dose-response relationship between increasing UAC and mortality. A higher UAC increased the risk of both CV and non-CV death after adjustment for other well-recognized CV risk factors, with the increase being significantly higher for CV mortality than for non-CV mortality ( $P=0.014$ ). A 2-fold increase in UAC was associated with a relative risk of 1.29 for CV mortality (95% CI 1.18 to 1.40) and 1.12 (95% CI 1.04 to 1.21) for non-CV mortality.

**Conclusions**—Urinary albumin excretion is a predictor of all-cause mortality in the general population. The excess risk was more attributable to death from CV causes, independent of the effects of other CV risk factors, and the relationship was already apparent at levels of albuminuria currently considered to be normal. (*Circulation*. 2002;106:1777-1782.)

**Key Words:** follow-up studies ■ mortality ■ risk factors

Epidemiological and experimental data show that high levels of urinary albumin excretion are associated with an increased incidence of all-cause and, in particular, cardiovascular (CV) mortality. This evidence comes from observations involving high-risk patients, such as those with diabetes and hypertension and the elderly, and in elderly subjects with a history of established CV disease.<sup>1-8</sup> The link between urinary albumin excretion and atherosclerotic disease is suggested to be found in dysfunction of the endothelium and its sequela. However, the relevance of urinary albumin excretion as a risk indicator in the general population is controversial. The few published studies on this topic have been for small populations, have relied on retrospectively collected data, or have been reported for groups of subjects who were referred because of suspected disease.<sup>5-7</sup> The

greater morbidity and poorer health status in these selected patient populations hamper the generalization of the results to the population at large. Therefore, in the present study, we address the question of a relationship between urinary albumin excretion and all-cause mortality and both CV and non-CV mortality in a large cohort selected from the general population.

## Methods

### Study Population

The Prevention of Renal and Vascular End Stage Disease (PREVEND) study is designed to prospectively investigate the natural course of increased levels of urinary albumin excretion and its relation to renal and CV disease in a large cohort drawn from the general population. Details of this protocol have been described

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**TABLE 1. Characteristics of Total Study Group**

Characteristic	Total Population	Mortality Status			Missing Subjects, n
		Alive	CV Death	Non-CV Death	
Subjects, N	40 548	40 032	178	338	
Age, y					
P50	48	48	68	65	
P5–P95	30–71	30–71	45–74	43–74	
Male, %	45.6	45.4	66.8	59.5	
Diabetes, %	2.6	2.5	7.9	10.1	129
Hypertension, %	11.2	11.0	38.1	22.3	1368
Hyperlipidemia, %	4.7	4.7	11.4	6.1	1744
Family history of CVD, %	32.1	32.1	43.2	29.8	2213
History of or actual smoking, %	42.2	42.1	47.7	54.1	252
Myocardial infarction, %	3.0	2.9	18.0	11.1	887
History of stroke, %	0.8	0.8	8.6	2.4	697
Morning UAC, mg/L					
P50	6.1	6.1	8.6	7.7	
P5–P95	2.3–28.7	2.3–27.9	2.3–240	2.3–104	
Microalbuminuria, %	7.2	7.0	22.5	16.0	

CVD indicates CV disease; P50, median; P5, 5th percentile; and P95, 95th percentile.

elsewhere.<sup>9,10</sup> In the period 1997 to 1998, all inhabitants of the city of Groningen (the Netherlands) aged 28 to 75 years (a total of 85 421 subjects) were sent a postal questionnaire and a vial to collect an early morning urine sample in which urinary albumin concentration (UAC) was measured; altogether, 40 856 subjects (47.8%) responded. The 1-page questionnaire collected information on the presence of established risk factors for CV disease and documented CV morbidity. Subjects were considered diabetic when they positively answered that they had a physician's diagnosis of diabetes, regardless of the type of antidiabetic treatment. Those who reported taking antihypertensive or lipid-lowering medication were regarded as hypertensive and hyperlipidemic, respectively. Subjects were classified as smokers if they reported smoking or having smoked cigarettes during the previous 5 years. A history of myocardial infarction or stroke was considered present if the subject reported having been hospitalized for at least 3 days because of that condition. A family history of CV disease was considered present if at least 1 first-degree relative had documented angina pectoris, myocardial infarction, or stroke before the age of 65 years.

All participants gave written informed consent. The PREVENT study was approved by the local medical ethics committee and was conducted in accordance with the guidelines of the Declaration of Helsinki.

### Urinary Albumin Measurements

Urinary albumin excretion was measured as UAC in a morning urine sample. UAC was determined by a commercial immunoturbidimetry assay with a sensitivity of 2.3 mg/L and interassay and intra-assay coefficients of variation of 4.4% and 4.3%, respectively (BNII, Dade Behring Diagnostica). Microalbuminuria was defined as a UAC between 20 and 200 mg/L, and macroalbuminuria was defined as a UAC >200 mg/L.<sup>11</sup>

### Mortality Data

From the time of recruitment, the vital status of the participants was checked through the municipal register. The cause of death was obtained by linking the number of the death certificate to the primary cause of death as coded by a physician from the Central Bureau of Statistics. Causes of death were coded according to the 10th revision of the International Classification of Diseases. Cause-specific end

points used in the analyses were CV disorders, and the remaining codes were those from non-CV causes.

Survival time for the participants was defined as the period from the date of the urine collection of the participant to the date of death from any cause or September 2000, until which date information about specific causes of death follow-up information was available. If a person had moved to an unknown destination, the date on which the person was dropped from the municipal registry was used as the census date.

### Statistical Analysis

To study the effects of albumin excretion on mortality, we fitted Cox proportional hazards models to the data. Two competing death causes were distinguished: CV and non-CV. Apart from UAC, the following available explanatory variables for CV and non-CV death were entered in the regression analysis: sex, age, presence of diabetes mellitus, use of antihypertensive drugs, use of lipid-lowering drugs, smoking, family history of CVD, previous myocardial infarction, and previous stroke. We used competing risk analysis, which allowed us to compare the effects of explanatory variables on either CV or non-CV death.<sup>12</sup> P-splines were used to explore the functional form of effects of continuous variables age and UAC. Results are summarized by hazard (risk) ratios, with CIs based on robust standard error estimates, by plotting the adjusted hazard ratio as a function of UAC and by plotting cause-specific cumulative incidence functions for specific covariate values.<sup>12</sup> A value of  $P < 0.05$  (2-sided) was used as the nominal level of statistical significance. We used the statistical package S-Plus 6 (2001, Insightful Co) for the analysis.

## Results

### Demographic and Clinical Characteristics

The total population sample consisted of 40 856 subjects. During the follow-up period, 518 cases were recorded. From these 518 deaths, 178 were classified as CV, and 340 were classified as non-CV, with the cause of death obtained from death certificates. The non-CV mortality group included 231 deaths from malignant neoplasm, 10 deaths from diabetes, and 99 deaths classified as being from various causes. For 73

**TABLE 2. Crude Incidence Rates per 1000 Person-Years (and 95% CIs) for All-Cause, CV, and Non-CV Mortality by UAC**

UAC	Mortality Status, Rate (95% CI)		
	Total Population	CV Death	Non-CV Death
0–10 mg/L	3.5 (3.1–3.9)	1.2 (1.0–1.5)	2.3 (2.0–2.8)
10–20 mg/L	4.5 (3.6–5.5)	1.3 (0.8–2.0)	3.2 (2.4–4.2)
20–200 mg/L	11.2 (9.1–13.7)	4.7 (3.2–6.6)	6.5 (4.8–8.7)
>200 mg/L	29.1 (19.3–43.7)	16.6 (8.9–29.1)	12.5 (5.9–24.7)
<i>P</i> for trend	<0.001	<0.001	<0.001

participants, the length of time on the study was not available. Urine samples could technically not be analyzed in 235 subjects. Two of these participants died from a non-CV cause. In total, 40 548 participants (of whom 516 had died) were available for the analysis. The median follow-up time was 961 days (maximum 1139 days).

Table 1 shows the baseline characteristics of the study cohort at the time of inclusion stratified into CV and non-CV mortality. Compared with those who survived, those who died were older, more likely to be male, and more likely to have had a history of diabetes, hypertension, hyperlipidemia, smoking, or a (parental) history of CV disease. Moreover, those who died from CV causes had the highest prevalences of these risk factors.

### Urinary Albumin Excretion and Mortality

Crude incidence rates per 1000 person-years for all-cause, CV, and non-CV mortality by different UACs are shown in Table 2. There was a clear dose-response relationship between UAC and all-cause, CV, and non-CV mortality ( $P$  for trend<0.001).

Table 3 summarizes the results of the Cox regression analysis adjusted for age and sex. Both CV and non-CV deaths were found to be associated with the presence or absence of diabetes mellitus, hyperlipidemia, smoking, myocardial infarction, and UAC level. CV deaths were also associated with a history of stroke. The effect of age on the

logarithmic hazard was found to be linear; the effect of UAC was linear after logarithmic transformation of UAC. A higher UAC increased the risk of both types of death, with the increase being significantly higher for the CV deaths ( $P=0.009$ ). The inclusion in the regression model of the other CV risk factors did not substantially alter the relationship between UAC and CV and non-CV death. In this mutually adjusted model, a 2-fold increase in UAC (ie, from 5 to 10 mg/L or 20 to 40 mg/L) was associated with a 1.29 higher risk for CV death and 1.12 higher risk for non-CV death ( $P=0.014$ ). Smokers tended to have an increased risk for non-CV death ( $P=0.039$ ). The effects of the level of UAC on the cause-specific hazards for CV and non-CV mortality, adjusted for all the risk factors as shown in Table 3, are presented in Figure 1. The solid line curves corresponding to the log-linear functional form lie within the dotted CI curves. This supports reasonability of the chosen model, although the (P-spline-based) CI curves obviously do not exclude the existence of a more complex functional relation. The increase in risk associated with an increase in UAC is steeper for CV deaths than for non-CV deaths.

To show the effects of UAC within the currently used reference ranges, cause-specific cumulative incidence functions using the Cox model were calculated for 2 UAC levels well below the lower border of the definition of microalbuminuria. The curves represent the cumulative incidence functions of CV and non-CV mortality for a nonhypertensive, nonhyperlipidemic, nondiabetic, nonsmoking 50-year-old male without a history of myocardial infarction or stroke, with UAC levels set equal to the 25th percentile (3.8 mg/L) and to the 75th percentile (9.8 mg/L). The 2-year cumulative incidence of CV mortality for a UAC of 3.8 mg/L is 0.12%, and that for a UAC of 9.8 mg/L is 0.15%, whereas for non-CV mortality, these figures are 0.21% and 0.24%, respectively (Figure 2).

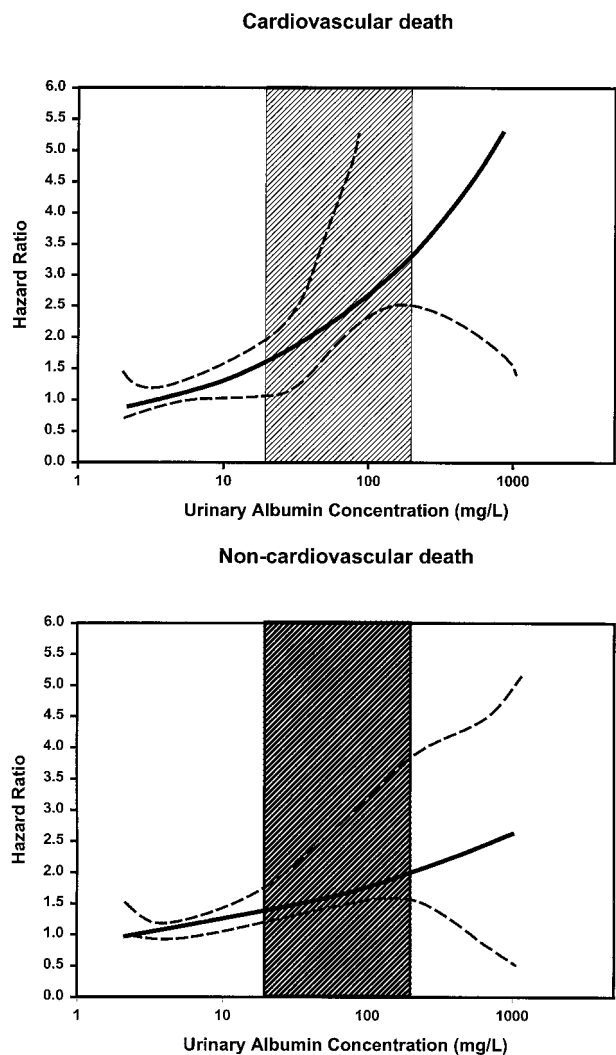
### Discussion

This is the first study to show that urinary albumin excretion is a strong predictor of all-cause mortality in the general

**TABLE 3. Cox Regression: Cause-Specific Hazard (Risk) Ratios**

Variable	Adjusted for Age and Sex				Mutually Adjusted for Multiple Risk Factors			
	RR	95% CI	<i>P</i>	<i>P</i> <sub>CV</sub>	RR	95% CI	<i>P</i>	<i>P</i> <sub>CV</sub>
Female sex					0.60	0.49–0.74	<0.001	
Age (per 10 y)					2.58	2.32–2.84	<0.001	
Hyperlipidemia	0.88	0.62–1.24	0.460		0.60	0.42–0.85	0.004	
Diabetes	1.89	1.35–2.65	<0.001		1.62	1.15–2.29	0.006	
Myocardial infarction	1.78	1.31–2.32	<0.001		1.84	1.37–2.46	<0.001	
Smoking								
CV	1.83	1.33–2.51	<0.001		1.65	1.19–2.27	0.002	
Non-CV	2.60	2.07–3.27	<0.001	0.073	2.49	1.97–3.16	<0.001	0.039
CV stroke	5.49	3.07–9.81	<0.001		4.01	2.20–7.30	<0.001	
UAC (doubling)								
CV	1.35	1.24–1.46	<0.001		1.29	1.18–1.40	<0.001	
Non-CV	1.17	1.09–1.25	<0.001	0.009	1.12	1.04–1.21	0.002	0.014

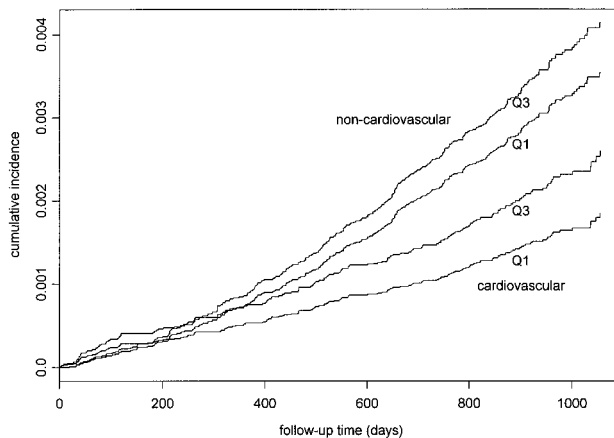
RR indicates risk ratio;  $P_{CV}$ , CV mortality vs non-CV mortality.



**Figure 1.** Adjusted effect of UAC on hazard function. Solid line shows estimated relation when logarithmic hazard is modeled as linear function of  $\log(\text{UAC})$ . Dotted lines are 95% confidence limits for more general functional relation, as estimated by P-splines. Hatched area represents upper and lower limit of current definition of microalbuminuria (20 to 200 mg/L).

population at large. The excess risk was significantly more attributable to death from CV causes than to death from non-CV causes and was independent from the effects of various well-recognized CV risk factors. Importantly, the relationship between UAC level and mortality was already apparent at the levels of albuminuria currently considered to be normal.

Microalbuminuria is associated with an increased risk of renal and CV morbidity and all-cause mortality in diabetic patients, in patients with hypertension, and in elderly subjects.<sup>1-8</sup> We found a stronger relationship between albuminuria and mortality from CV causes compared with non-CV causes in an unselected cohort derived from the population at large. In view of this finding, albuminuria appears to be a marker of generalized vascular disease and indicates an incremental risk for CV mortality not only in CV-compromised subjects. The precise cause underlying this



**Figure 2.** Cause-specific cumulative incidence functions of CV and non-CV mortality for nonhypertensive, nonhyperlipidemic, nondiabetic, nonsmoking 50-year-old males with no history of myocardial infarction or stroke, with UAC levels set equal to 25th percentile (quartile 1 [Q1], 3.8 mg/L) and 75th percentile (quartile 2 [Q3], 9.8 mg/L).

mechanism is unknown. It is possible that the glomerular albumin leak reflects a widespread atherosclerosis-mediated capillary vasculopathy.<sup>13-15</sup> Dysfunction of the coagulation and fibrinolytic systems has also been suggested as a possible link between microalbuminuria and CV disease. In diabetic and nondiabetic subjects, microalbuminuria has been associated with changes in von Willebrand factor, fibrinogen, thrombomodulin, and plasminogen activator inhibitor-1.<sup>16-18</sup> However, urinary albumin excretion is associated with several other risk factors that may themselves be linked with mortality. These include diabetes mellitus, hyperglycemia, hypertension, renal dysfunction, dyslipidemia, hyperhomocystinemia, dietary protein, smoking, and markers of an acute-phase response. A critical question within this context is whether the relationship between urinary albumin excretion and mortality is due to an association of urinary albumin excretion with other predictors of mortality. If albuminuria and the other prognostic factors share a common causal pathway, adjustment for these factors may attenuate the relationship between albuminuria and mortality. However, even after adjustment for these factors, albuminuria remains a relatively strong predictor after full adjustment, suggesting an independent additive component in the relationship between albuminuria and mortality from CV causes.

We also observed an association, although less strong, between albuminuria and non-CV mortality. The incidence of non-CV mortality could mostly be attributed to death due to malignant neoplasms. An elevated urinary albumin excretion in patients with malignancies has been reported previously.<sup>19</sup> Interestingly, although the precise underlying mechanism is unknown, it has been speculated that in this type of patient, the increased urinary albumin loss appears to be more of an isolated renal phenomenon than to be related to endothelial dysfunction, because a normal endothelial function was observed, as demonstrated by the transcapillary escape rate of albumin, which suggests an overall unaffected capillary permeability.

The present study adds considerable data to the available information on urinary albumin excretion as a vascular risk factor because we have used the full range of UAC in studying the relationship with mortality and did not cluster UAC levels into several categories. Several objections could be raised about categorizing UAC, including the following: (1) a step function is biologically implausible because estimating the risk of categories ignores the possibility that actual risk varies smoothly with the exposure of the risk factor; (2) high-risk individuals will be submerged in a pool of lower-risk members, thereby diluting the effect size; (3) there may be a significant loss of power, especially when the effects are concentrated at the end of the UAC scale; and (4) cutoff point bias may be introduced when cutoff points are selected to maximize effect size.

It has been suggested in selected patient populations that even modestly raised albuminuria values, within what hitherto has been considered the normal range, are associated with a future risk of CV events.<sup>3,5,20</sup> Our finding of a dose-response relationship between UAC and the risk of mortality extends such a suggestion to the general population. Therefore, we suggest that the lower limit defining a “pathological” albuminuria seems appropriate.

The present study has a number of limitations, and to appreciate the findings, some issues need to be addressed. We measured UAC only once and without correcting for potential variability in urine concentration. In addition, we were unable to perform detailed measurements of the CV risk factors. Self-reported histories have limitations because a certain degree of misclassification; therefore, bias may occur. Because we do not expect this misclassification to be related to the risk factors or to the morning urinary albumin measurements themselves, misclassification would dilute the estimated effects; ie, it would make the estimated risk ratio closer to 1. Therefore, our analysis may have underestimated the true association between urinary albumin excretion and mortality. The relatively short follow-up could have masked some of the long-term health hazards of an increased urinary albumin excretion. The current large population-based study is not characterized by a high participation rate and, hence, could be subject to selection bias. However, the finding that ≈40% of all deaths in the present study were classified as being due to CV disease, which is in line with previous prospective studies of subjects of the general population, favors acceptable generalizability.<sup>21</sup> Finally, we did an extensive subgroup analysis on the other investigated risk factors but did not find any significant differences. However, although the total number of studied subjects is very large, the number of subjects who died is relatively small, suggesting that the present study is likely underpowered in its design to reliably detect any differences in subgroups.

We conclude from this large prospective cohort study that albuminuria is an important marker for both CV and non-CV mortality. The use of UAC as a screening tool is made more feasible by more sensitive assays that are commercially available and that appear to be reliable even in the lower ranges. However, mechanisms underlying the increased CV risk of an increased urinary albumin excretion require further elucidation. There may be an important clinical role for

albuminuria in CV disease screening that is analogous to the role of blood pressure and lipid screening. Because albuminuria is a modifiable risk marker, because studies of secondary prevention have shown that blood pressure-lowering drugs effectively reduce the albumin excretion rate, and because ACE inhibitors seem to be particularly effective, the current observation may lead to new therapeutic strategies in the prevention of CV disease.

## Appendix

### PREVEND Study Group

In addition to the authors, the PREVEND investigators are as follows: Department of Internal Medicine (Division of Nephrology), University Hospital of Groningen: G.J. Navis, MD; R.T. Gansevoort, MD; and J. Mulder MD; Department of Internal Medicine, University Hospital of Groningen: A.J. Smit, MD; S.J.L. Bakker, MD; and A.M. van Roon, PhD; Department of Cardiology, University Hospital of Groningen: A.J. van Boven, MD; Department of Clinical Pharmacology, University of Groningen: R.H. Henning, MD; Department of Medical Statistics, University of Groningen: J.G.M. Burgerhof, MSc; Trial Coordination Center, University Hospital of Groningen: C. Balje, MSc; Department of Social Pharmacy and Pharmacoepidemiology, University of Groningen: L.T.W. de Jong-van den Berg, PhD, and M.J. Postma, PhD; Department of Medical Genetics, University of Groningen: G.J. te Meerman, PhD; Department of Medical Physiology: J.H.J. Muntinga, PhD; and Municipal Health Department, Groningen, the Netherlands: Jan Broer, MD.

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