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Microalbuminuria is common, also in a nondiabetic, nonhypertensive population, and an independent indicator of cardiovascular risk factors and cardiovascular morbidity

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Abstract. Hillege HL, Janssen WMT, Bak AAA, Diercks GFH, Grobbee DE, Crijns HJGM, van Gilst WH, de Zeeuw D, de Jong PE for the PREVEND Study group (University of Groningen and University Hospital Groningen, Groningen; University Medical centre, Utrecht, the Netherlands). Microalbuminuria is common, also in a nondiabetic, nonhypertensive population, and an independent indicator of cardiovascular risk factors and cardiovascular morbidity. *J Intern Med* 2001; **249:** 519–526.

Objectives. To assess the prevalence of microalbuminuria in the general population, especially in nondiabetic and nonhypertensive subjects, and its association with known cardiovascular risk factors and cardiovascular morbidity.

Design. Cross-sectional cohort study.

Setting. Inhabitants of the city of Groningen, the Netherlands.

Subjects. All inhabitants, aged between 28 and 75 years, were send a postal questionnaire and a vial to collect an early morning urine sample ($n = 85\ 421$). Of these 40 856 subjects (47.8%) responded. Cardiovascular risk factors and morbidity were validated in a well defined nondiabetic and nonhypertensive group of 5241 subjects.

Main outcome measures. Microalbuminuria, self-reported cardiovascular risk and cardiovascular morbidity in the total study cohort, and additionally more detailed measurements in a subset of the total population.

Results. Microalbuminuria (20–200 mg L^{-1}) was present in 7.2% of the subjects and independently associated with age, gender, hypertension, diabetes, smoking, previous myocardial infarction and stroke. Some of these associations were already observed at albuminuria levels of 10–20 mg L^{-1}. After exclusion of the diabetic and hypertensive subjects, microalbuminuria was still prevalent in 6.6% of the subjects.

Conclusions. Microalbuminuria appears to be common not only in the general population but also in a nondiabetic, nonhypertensive population and is independently associated with increased cardiovascular risk factors and cardio- vascular morbidity. Importantly, some of these associations are present at urinary albumin levels currently considered to be normal. These findings suggest that urinary albumin measurements may be useful in early risk profiling and prevention of cardiovascular disease in the population at large.

Keywords: albuminuria epidemiology, cardiovascular diseases diagnosis, cross sectional studies, population, risk factors.

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Introduction

Microalbuminuria is associated with an increased risk for renal and cardiovascular morbidity and mortality in diabetic patients [1–5], patients with hypertension [6–12] and in elderly subjects [13, 14]. In a recent study it is suggested that an increased urinary albumin excretion is associated with an increased risk of ischaemic heart disease in subjects without renal and ischaemic heart disease or diabetes mellitus [15]. However, the significance of microalbuminuria as a common independent risk factor in a nondiabetic, nonhypertensive population is still a matter under debate which needs to be solved in view of the potential significance of microalbuminuria as a risk factor. Reliable data on the prevalence of microalbuminuria in the general population and its association with cardiovascular risk factors and cardiovascular morbidity is limited. The relevance of previous research to the general population is debated because most published data to date have been derived from small studies or subjects who were referred because of suspected disease [16–20]. The aim of the present large population based study was to determine the prevalence of microalbuminuria in the general population and its relationship with cardiovascular risk factors and morbidity. In addition, we have investigated whether these associations were present at levels of urinary albumin excretion currently considered to be 'normal'. Results were validated in a nondiabetic, nonhypertensive sample from the population in which more detailed measurements were obtained.

Methods

Study population

The PREVEND (Prevention of REnal and Vascular ENd stage Disease) study was designed to prospectively investigate the natural-course of microalbuminuria and its relation with renal and cardiovascular disease in a large cohort drawn from the general population. All inhabitants of the city of Groningen (the Netherlands), between the age of 28–75 years, in total 85 421 subjects, were sent a postal questionnaire and a vial to collect an early morning urine sample, and altogether 40 856 people (47.8%) responded. The one-page questionnaire provided information on the presence of the established risk factors for cardiovascular disease and documented cardiovascular morbidity. Subjects were considered being diabetic when they positively answered the question whether they had a physician diagnosis of diabetes, regardless of the type of antidiabetic treatment. Those who reported taking antihypertensive or lipid lowering medication were regarded as hypertensive and hyperlipidaemic, 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 cardiovascular disease was considered present if at least one first degree relative had documented angina pectoris, myocardial infarction or stroke before the age of 65 years.

Sample of population in which more detailed measurements were obtained

We determined robustness of results by performing a similar analysis comprising a selection of the nondiabetic and nonhypertensive subjects that visited the outpatient clinic. This study cohort consists of all responding subjects with a morning urinary albumin concentration of 10 mg L^{-1} or above together with a randomly selected control group of the total study population with morning urinary albumin excretion of <10 mg L^{-1}, and who are willing to participate in a long-term natural course programme. Details of this protocol have been described elsewhere. In this natural-course programme the subjects were at baseline examined on two occasions within a week. The examination consisted of blood pressure measurements (with an automatic Dinamap device), electrocardiography and collection of two consecutive 24 h urine specimens for accurate albumin measurements. Blood samples were taken to determine plasma levels of glucose and cholesterol. Insulin using diabetic subjects and pregnant women were excluded. All subjects ($n = 8592$) completed the baseline measurements of the natural-course programme.

Systolic and diastolic blood pressure measurements were calculated as the mean of the last two out of 10 successive measurements of the two visits.

Hypertension was defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure of ≥90 mmHg or the use of antihypertensive medication. Diabetes was defined using impaired glucose tolerance criteria; fasting glucose levels of ≥6.1 mmol L^{-1} or nonfasting plasma glucose level of 7.8 mmol L^{-1}, or the use of oral antidiabetic drugs. Hyperlipidaemia was defined as a total serum cholesterol concentration of ≥6.5 mmol L^{-1}, or in the case of a previous myocardial infarction ≥5.0 mmol L^{-1}, or the use of lipid lowering medication. A myocardial infarction was defined as reported hospitalization or electrocardiographic evidence of myocardial infarction according to the Minnesota criteria [21]. The nondiabetic and nonhypertensive subgroup consisted of 5421 subjects.

Urinary albumin measurements

Morning urinary albumin concentration (MUAC) was determined by a commercial immunoturbidimetry assay with sensitivity of 2.3 mg L^{-1} and inter- and intra-assay coefficients of variation of 4.4 and 4.3%, respectively (Dade Behring Diagnostica). Urine samples could not be analysed for 237 of the 40 856 subjects. The number of the studied subjects was thus reduced to 40 619. Microalbuminuria is conventionally defined as a urinary albumin excretion between 30 and 300 mg per 24 h for timed 24 h urine collections. Microalbuminuria can be defined for untimed samples as urinary albumin excretion between 20 and 200 mg L^{-1} [22]. Subjects with the morning urinary albumin concentration of 10–20 mg L^{-1} were considered to have 'high-normal' albuminuria and those with less than 10 mg L^{-1} were regarded to have 'low-normal' albuminuria. Of the 8592 subjects who completed the natural-course programme 433 subjects were excluded because of erythrocyturia or leucocyturia (erythrocytes >50 μL^{-1} or leucocytes >75 μL^{-1}, or leucocytes = 75 μL^{-1} and erythrocytes >5 μL^{-1}). In this group albuminuria was expressed as the mean value for two 24 h urine collections. Microalbuminuria was defined as 30–300 mg per 24 h, 'high-normal' as 15–30 mg per 24 h and 'low-normal' as 0–15 mg per 24 h.

Statistical analysis

Differences in proportions were tested using χ^2 analysis and Fisher's exact test. Age and sex-adjusted prevalence rates were calculated by the direct method. Age categories were below 39, 40–49, 50–69 and 70 years and older. The age and sex distribution in the total study group was used as the standard population. Logistic regression analysis was performed to predict microalbuminuria from cardiovascular risk and morbidity factors, sex and age. Patients with a urinary albumin concentration above 200 mg L^{-1} for the total study population and above 300 mg per 24 h for the subgroup of the total population were excluded from these analyses. Because the subgroup was not a simple random sample of the total study population these data were analysed using a 'design-based' logistic regression analysis that takes the sample design into account.

Odds ratios were taken as approximation of relative risk and expressed with 95% CI. All *P*-values are two tailed. Analyses were performed using the statistical packages SPSS version 8.0, SAS version 6.12 and for the 'design-based' logistic regression analysis STATA 6.0.

Results

Microalbuminuria (20–200 mg L^{-1}) was present in 7.2% [95% CI 6.9–7.4%] of the subjects. In 282 subjects (0.7%) [0.6–0.8%] a morning urinary albumin concentration higher than 200 mg L^{-1} was found. The group-specific characteristics of the 40 619 subjects according to albuminuria are given in Table 1. Advanced age, male sex and the presence of diabetes, hypertension, hyperlipidaemia, smoking, myocardial infarction and stroke were seen more frequent in subjects with increased levels of albuminuria.

Figure 1 shows age and sex adjusted prevalences of microalbuminuria in diabetic, in hypertensive subjects and in nonhypertensive nondiabetic subjects. Although micro- and macroalbuminuria were found more frequently in the diabetic and hypertensive subgroup, microalbuminuria was still prevalent in 6.6% of the nondiabetic, nonhypertensive subjects. Out of 2918, 2186 (74.9%) subjects with microalbuminuria and 5682 (84.2%) out of 6749 subjects with 'high-normal' albuminuria reported not to have diabetes and/or hypertension.

The associations between microalbuminuria and various cardiovascular risk factors in the total study population are shown in Table 2. A morning

Table 1 Characteristics of the total study population

Urinary albumin excretion	0–10 mg L^{-1} (n = 30 670)	10–20 mg L^{-1} (n = 6749)	20–200 mg L^{-1} (n = 2918)	>200 mg L^{-1} (n = 282)	Total (n = 40 619)
Mean age in years (SD)	49.4 (12.7)	47.9 (12.9)	53.1 (13.2)	57.2 (12.7)	49.5 (12.9)
Male (%)	43.4	51.5	53.8	59.2	45.6
Median (25–75th percentile) morning urine albumin concentration (mg L^{-1})	4.9 (3.2–6.9)	12.7 (11.1–14.9)	32.7 (24.6–54.0)	351.0 (254.0–654.0)	6.1(3.8–9.9)
Diabetes (%)	2.1	2.9	6.2	17.6	2.6
Hypertension (%)	10.3	10.9	18.9	38.1	11.2
Hyperlipidaemia (%)	4.5	4.4	6.7	17.2	4.7
Positive family history of cardiovascular disease (%)	32.0	31.7	33.2	40.9	32.1
Smoking (%)	40.0	48.8	49.4	48.2	42.2
Myocardial infarction (%)	2.7	2.8	6.0	11.0	3.0
Stroke (%)	0.7	0.8	1.6	4.7	0.8

urinary albumin concentration in the microalbuminuric range was associated with age and sex and the presence of diabetes, hypertension, smoking, previous myocardial infarction or stroke but not with a family history of cardiovascular disease. The independent contribution of the various risk factors and age and sex was further explored by modelling microalbuminuria as dependent variable in a mutually adjusted model. Only hyperlipidaemia remained not significant in the mutually adjusted model.

We also examined in the total study population the association between a level of urinary albumin excretion nowadays considered to be normal and the cardiovascular risk factors of interest. Relative risks for age, sex, diabetes, hypertension and smoking were already increased in the group with 'high-normal' albuminuria (10–20 mg L^{-1}) compared with the group with a urinary albumin excretion level between 0 and 10 mg L^{-1}, although hypertension was not significant in the univariate analysis (Table 2).

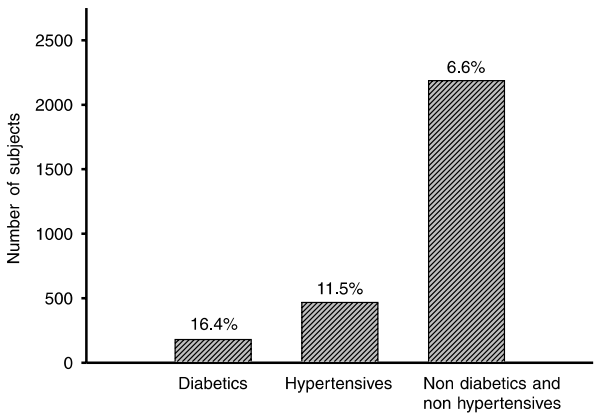

Fig. 1 Age and sex adjusted prevalences of microalbuminuria in diabetic, in hypertensive, and in nondiabetic nonhypertensive subjects.

The group-specific characteristics of the 5421 nondiabetic and nonhypertensive subjects in which more detailed measurements were obtained are presented in Table 3. Table 4 describes the associations in this subset of the total population. The point estimates of the relative risks were rather similar for the majority of cardiovascular risk factors and morbidity parameters, when compared with the total population, whereas the 95% CI were considerably larger. The association with microalbuminuria remained statistically significant for age, sex and stroke in the multivariate analysis.

Discussion

Microalbuminuria is common in the general population with a prevalence of 7.2% and independently associated with cardiovascular risk factors and cardiovascular morbidity. The majority of these microalbuminuric subjects (74.9%) has no reported diabetes or hypertension. The results show that even after excluding the diabetic and hypertensive subjects microalbuminuria is still prevalent in 6.6% of the subjects. Cardiovascular risk factors were already elevated at levels of albuminuria currently considered to be normal (10–20 mg L^{-1} or 15–30 mg per 24 h).

To appreciate these findings some issues need to be addressed.

Current opinions about the prevalence of microalbuminuria in a general population are based on a

Table 2 Univariate and mutually adjusted relative risks for presence of microalbuminuria versus 0–20 mg L^{-1} albuminuria, 'high-normal' (10–20 mg L^{-1}) versus 'low-normal' (0–10 mg L^{-1}) and indicators of cardiovascular risk for the total study population

	Microalbuminuria versus 0–20 mg L^{-1} albuminuria (n = 40 337)		'High-normal' versus 'low-normal' albuminuria (n = 37 419)	
	Univariate RR (95% CI)	Mutually adjusted RR (95% CI)	Univariate RR (95% CI)	Mutually adjusted RR (95% CI)
Age (per year)	1.02 (1.02–1.03)***	1.02 (1.01–1.03)***	0.99 (0.99–1.00)***	0.99 (0.98–0.99)***
Male	1.43 (1.32–1.54)***	1.42 (1.31–1.55)***	1.38 (1.31–1.46)***	1.36 (1.28–1.44)***
Diabetes (yes/no)	2.93 (2.48–3.46)***	2.08 (1.70–2.53)***	1.41 (1.19–1.66)***	1.56 (1.29–1.89)***
Hypertension (yes/no)	2.00 (1.81–2.21)***	1.46 (1.28–1.65)***	1.07 (0.98–1.16)	1.28 (1.16–1.42)***
Hyperlipidaemia (yes/no)	1.55 (1.32–1.81)***	0.96 (0.79–1.16)	0.98 (0.86–1.12)	0.96 (0.82–1.12)
Positive family history of cardiovascular disease (yes/no)	1.06 (0.97–1.14)	0.95 (0.87–1.04)	0.98 (0.93–1.04)	0.97 (0.91–1.03)
Smoking (yes/no)	1.37 (1.27–1.48)***	1.58 (1.45–1.72)***	1.43 (1.36–1.51)***	1.38 (1.30–1.47)***
Myocardial infarction (yes/no)	2.30 (1.94–2.72)***	1.29 (1.04–1.60)*	1.03 (0.88–1.21)	1.05 (0.86–1.28)
Stroke (yes/no)	2.19 (1.60–3.00)**	1.58 (1.10–2.26)*	1.12 (0.83–1.51)	1.11 (0.79–1.56)

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

Table 3 Characteristics of the subset of the population in which more detailed measurements were performed and in which diabetic and hypertensive subjects were excluded

Urinary albumin excretion	0–15 mg L^{-1} (n = 4280)	15–30 mg L^{-1} (n = 581)	30–300 mg L^{-1} (n = 355)	>300 mg L^{-1} (n = 25)	Total (n = 5241)
Mean age in years (SD)	43.9(10.7)	46.0(11.6)	48.3 (12.4)	50.0 (14.7)	44.5 (11.0)
Male (%)	44.9	55.2	55.5	68.0	46.9
Median (25–75th percentile) morning urine albumin concentration (mg L^{-1})	7.0(5.5–9.4)	19.7(16.8–22.7)	46.9 (36.8–79.7)	532.5(352.6–981.4)	7.9(5.8–12.3)
Hyperlipidaemia (%)	18.9	19.6	26.3	37.5	19.6
Positive family history of cardiovascular disease (%)	28.5	29.2	32.0	40.0	28.9
Smoking (%)	39.9	44.9	46.5	32.0	40.8
Myocardial infarction (%)	3.7	4.7	7.7	8.7	4.1
Stroke (%)	0.5	0.2	2.0	0.0	0.9

number of studies. Reported prevalences vary significantly because of variations in ethnic groups, specimen collection, the cut-off level of albumin excretion and analytical methods. The distribution of demographic and coexisting diseases may also contribute. In addition, the studies are limited in size and not strictly population-based, which limits the general applicability of the results. In case we restrict ourselves to studies performed in the Western European population four 'general population' studies reported prevalences of microalbuminuria in ranges from 2.2 to 10.2% [13, 16, 18, 23]. However, the number of included subjects ranges from 171 to 1684 subjects and may not reflect the situation in the general population. In one relatively large nonEuropean study, which included also 4330 European subjects, a prevalence of 2.7% was reported, but the definition for microalbuminuria was based on a cut-off value of 30 mg L^{-1} [18]. In case we use their criteria the prevalence of microalbuminuria in our study is reduced to 4.5%. Our study group is significantly larger, unselected and covers a wide age range, thus providing not only an adequate estimate of the prevalence of microalbuminuria in the general adult population but also in subgroups as nondiabetic, nonhypertensive subjects.

The clinical relevance of microalbuminuria as a common independent risk indicator in the absence of diabetes and hypertension is still unestablished. A number of studies, addressed as being a sample of the general population, showed cross-sectionally and longitudinally that microalbuminuria is independently associated with an adverse cardiovascular risk profile and increased cardiovascular risk [14–19, 23–25]. However, most published data are small sized, excluded not on purpose diabetic and hyper-

Table 4 Mutually adjusted relative risks for presence of microalbuminuria and 'high normal' (15–30 mg per 24 h) albuminuria and indicators of cardiovascular risk in the subset of well defined nondiabetic nonhypertensive subgroup

	Microalbuminuria versus 0–30 mg per 24 h albuminuria (5216)		'High-normal' versus 'low-normal' albuminuria (4861)	
	Univariate	Mutually adjusted	Univariate	Mutually adjusted
Age (per year)	1.03 (1.01–1.04)***	1.03 (1.01–1.04)	1.01 (1.00–1.03)*	1.01 (0.99–1.03)
Male	1.40 (1.06–1.86)*	1.39 (1.04–1.85)*	1.43 (1.11–1.87)**	1.35 (1.03–1.77)*
Hyperlipidaemia (yes/no)	1.40 (1.02–1.94)*	1.08 (0.80–1.44)	0.99 (0.71–1.38)	0.94 (0.67–1.33)
Positive family history of cardiovascular disease (yes/no)	1.19 (0.95–1.49)	1.12 (0.87–1.43)	1.09 (0.86–1.39)	1.02 (0.79–1.32)
Smoking (yes/no)	1.21 (0.92–1.59)	1.25 (0.94–1.66)	1.22 (0.94–1.58)	1.18 (0.90–1.56)
Myocardial infarction (yes/no)	1.68 (1.07–2.63)*	1.42 (0.89–2.27)	1.40 (0.76–2.61)	1.40 (0.73–2.70)
Stroke (yes/no)	3.26 (1.29–8.26)**	3.29 (1.23–8.80)*	0.20 (0.02–1.48)	0.21 (0.03–1.71)

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

tensive subjects and were mainly derived from subjects that were referred because of suspected disease, which limits extrapolation of the results to the general population. This study is the first that shows an independent association between urinary albumin excretion and cardiovascular risk factors not only in the population at large but also in a strict nondiabetic nonhypertensive subset of the general population. The higher prevalence of microalbuminuria in men, and the finding that microalbuminuria is age dependent is in agreement with previous reports [16, 18, 19, 23]. The association between urinary albumin excretion and several cardiovascular disease risk factors was apparent already in albuminuria ranges currently considered to be 'normal'. Several studies have shown a gradual relationship between levels of urinary albumin in microalbuminuria-ranges (30–300 mh per 24 h) and cardiovascular risk factors [6–9, 12, 17, 26]. Although it has been speculated that urinary albumin excretion levels relevant for cardiovascular disease might be lower, no studies so far focused on lower urinary albumin excretion rate levels. Our results demonstrate that high-normal albuminuria is associated with diabetes, hypertension and smoking. Therefore, reconsideration of the lower limit defining a 'pathological' albuminuria is strongly suggested.

Our study has some limitations. In the overall cohort we have only measured urinary albumin concentrations without correcting for potential variability in urine volumes. Previous studies have shown that the early morning spot urine gives a good estimate of the 24-h urinary excretion of albumin [22, 27, 28]. Furthermore, an early morning urine sample allows screening in large populations. We therefore feel it to be a reliable index of urinary albumin excretion in a population-based study. Moreover, the analysis of the validation set, in which more accurate measurements were performed (two times 24 h urine collections), confirmed the findings from the total study cohort.

The response rate, although lower than might be achieved in research conducted in a clinical setting, is reasonable for a postal survey. However, the male to female ratio and the mean age were different for the responders versus nonresponders (45.6% males in responders versus 54.6% in nonresponders; mean age for responders was 51.9 years and 46.4 years for nonresponders). The effect this may have on the reported outcome is unclear.

Self-reported histories have limitations because misclassification and therefore bias may occur. However, we do not believe that this has materially affected the results because the factors that were associated with microalbuminuria in the total study cohort showed similar trends as the sample of the total population in which more detailed measurements were performed and strict nondiabetic, nonhypertensive subjects were included. The estimated CI in this subgroup were considerably larger because of a reduced sample size and the utilization of a 'design-based analysis' [29, 30]. Most of the statistical packages assume that the data have been selected by simple random sampling and consider the data as being independent and identically distributed. This may lead to grossly underestimated CI and in some situations biased point estimates. Our subgroup was not a random sample but a stratified sample of the total population selecting all the subjects with a 'high-normal' urine albumin excre-

tion and a control group characterized with a 'low-normal' urine albumin excretion.

A cross-sectional design limits the ability to causally relate albuminuria and cardiovascular risk factors and cardiovascular morbidity. Further longitudinal research is necessary to determine whether albuminuria contributes independently to cardiovascular morbidity and mortality also in nondiabetic, nonhypertensive subjects. Ongoing follow-up studies of the PREVEND natural course cohort will answer these questions.

We conclude from this cross-sectional study that microalbuminuria is far from being rare and an important indicator for cardiovascular risk factors and cardiovascular morbidity also in nondiabetic, nonhypertensive subjects. Further prospective studies are needed to assess the relationship between the occurrence of microalbuminuria and the subsequent risk of cardiovascular disease. Eventually, the measurements of urine albumin excretion may prove to be useful in early risk profiling and prevention of cardiovascular disease and may lead to new therapeutic strategies in the prevention of cardiovascular disease.

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