Cardiovascular Risk Factors Are Differently Associated with Urinary Albumin Excretion in Men and Women

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Abstract. Cardiovascular morbidity and mortality is not equally distributed among genders, men being more affected than women. It is not clear whether this is only related to a higher prevalence of the cardiovascular risk factors or to a similar prevalence of the risk factors as in women but a greater vascular susceptibility to these risk factors in men. This was tested by studying the association between various cardiovascular risk factors and urinary albumin excretion (UAE) in a large cohort of male and female subjects. While the prevalence of smoking and hypercholesterolemia was comparable between the genders, obesity was more common in women, and diabetes and hypertension were more frequent in men. The prevalence of microalbuminuria was about twofold higher in men. Interestingly, for a given level of any risk factor, UAE was higher in men than in women. On multivariate analysis with UAE as the dependent variable, an interaction with gender was found for the risk factors age, body mass index, and plasma glucose. Thus, for a higher age, body mass index, and glucose, the UAE is significantly increased in men when compared with women. It is concluded that gender differences exist in the association between cardiovascular risk factors and UAE. This is consistent with a larger vascular susceptibility to these risk factors in men as compared with women.

Cardiovascular risk differs between men and women. Men have a higher cardiovascular morbidity and mortality than women (1,2). The lifetime risk of developing coronary heart disease is one in two for men and one in three for women (3). This raises the question why men are more prone to cardiovascular morbidity and mortality. Is it because the prevalence of cardiovascular risk factors, such as hypertension, obesity, diabetes, and smoking, is higher in men? Or is the vasculature in men more sensitive to a given risk factor than in women, or is it a combination of both (1,4)? An increased urinary albumin excretion (UAE) is considered as a marker of damage of the vascular endothelium, the latter being the underlying cause of cardiovascular diseases, and it has been shown that an elevated UAE is associated with a higher cardiovascular morbidity and mortality (5–7). Interestingly, the prevalence of microalbuminuria is higher in men than in women (8–11).

We hypothesize that the known cardiovascular risk factors have a more harmful effect on the vascular endothelium in men as compared with women. We tested this hypothesis by studying the association between cardiovascular risk factors and UAE in a large cohort of male and female subjects, as part of the PREVEND study.

Material and Methods

Study Design and Population

As part of the PREVEND study (Prevention of Renal and Vascular End-Stage Disease), all inhabitants of the city of Groningen, the Netherlands, aged between 28 to 75 yr were asked to answer a short questionnaire and send in a morning urine sample. The aim of the PREVEND study is to determine the relation between microalbuminuria (the dichotomized parameter of elevated UAE) and cardiovascular and renal disease in the general population (12). Pregnancy and insulin treatment were exclusion criteria. A total of 40,856 subjects responded. All subjects with a urinary albumin concentration of $\geq$ 10 mg/L (n = 7768) and a random sample of subjects with an albumin concentration $<$ 10 mg/L (n = 3395) were invited to an outpatient clinic. The screening program was completed by 8592 subjects. They filled in a questionnaire giving demographics, cardiovascular and renal history, smoking status, and the use of oral antidiabetic, antihypertensive, and antilipidemic drugs. Anthropometrical measurements were performed, and BP was measured for 10 min on 2 d with an automatic Dinamap XL Model 9300 series device (Johnson-Johnson Medical Inc., Tampa, Florida). Fasting blood samples were taken, and subjects collected urine for two consecutive periods of 24 h. For the present analyses, 78 subjects were excluded because of a history of renal disease or proteinuria, 445 subjects because of leucocyturia or erytrocyturia, according to dipstick analysis (leukocytes $>$ 75/μl or erythrocytes $>$ 50 erythrocytes/μl, or leukocytes = 75 and erythrocytes $>$ 5/μl), and 228 subjects because of missing information on one of the variables included in the regression model. This left 7841 subjects for the present analyses. All subjects gave written informed

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consent. The local medical ethics committee approved the PREVEND study, and the conduct of the project was in accordance with the guidelines of the declaration of Helsinki.

Measurements and Definitions

Creatinine assessments in blood and urine and plasma cholesterol and glucose were determined in one laboratory by Kodak Ektachem dry chemistry (Eastman Kodak, Rochester, NY), an automated enzymatic method. Urinary leukocyte and erythrocyte measurements were done by Nephur-test + leuco sticks (Boehringer Mannheim, Mannheim, Germany). Urinary albumin concentration was determined by nephelometry with a threshold of 2.3 mg/L and intra-assay and inter-assay coefficients of variation of less than 2.21% and 2.64%, respectively (Dade Behring Diagnostic, Marburg, Germany). Urinary albumin excretion (UAE) is given as the mean of the two 24 h urine excretions. Creatinine clearance is given as the mean of two 24-h urinary creatinine excretions divided by plasma creatinine. The creatinine clearance was not corrected for body surface area because we corrected in the regression model for height and weight. Body mass index (BMI) was calculated as weight (kg) divided by square of height (m^2). Obesity was defined as a BMI $>$ 30 kg/m^2. Waist-to-hip ratio (WHR) was calculated as the ratio of minimal waist circumference and maximal hip circumference. BP values given are the mean of the last two recordings of both days. The following criteria were used for the definition of hypertension: systolic BP (SBP) of $\geq$ 140 mmHg or diastolic BP (DBP) of $\geq$ 90 mmHg or the use of antihypertensive medication. Smoking was defined as current smoking or cessation of smoking less than 1 yr before the study. Diabetes was defined as a fasting plasma glucose level of $\geq$ 7.0 mmol/L and a nonfasting plasma glucose level of $\geq$ 11.1 mmol/L or the use of oral antidiabetic drugs. Hypercholesterolemia was defined as serum cholesterol of $\geq$ 6.5 mmol/L, or $\geq$ 5.0 mmol/L if the subject had a previous myocardial infarction, or the use of lipid lowering medication. The definition of microalbuminuria is a UAE of 30 to 299 mg/24 h.

Statistical Analyses

We first compared the variables of interest between the genders. A *t* test was used to test the null hypothesis that the means of the variables are equal for each gender. A χ^2 test examined if the distribution of the categorical variables differed between the genders. The Mann-Whitney test, a nonparametric test, was used for UAE because of its skewed distribution.

The aim of the second analysis was to identify which factors (age, systolic and diastolic BP, BMI, WHR, plasma glucose, cholesterol, creatinine clearance, smoking, use of antihypertensive, lipid-lowering, and antidiabetic medication), with special attention to the impact of gender, are important predictors of UAE. For the screening of the PREVEND study, we overselected subjects with an elevated UAE to acquire sufficient subjects with microalbuminuria. To overcome this oversampling of subjects with elevated UAE in the present study, a design-based analyses was performed. Due to this weighting method, our conclusions can be generalized for the general population. The design-based linear regression model was built with STATA (version 7.0). The dependent variable in the model was UAE. Graphical inspection of UAE showed a skewed distribution. A double natural logarithm transformation gave the optimal residual analysis. After the double natural logarithm transformation, visual inspection of the data revealed a curved relationship between UAE and some of the explanatory variables. Examining of the curvature was done by graphical interpretation and by including a quadratic term of the variable and tests its inclusion in the model using the linear regression model. For optimal residual analysis plasma glucose was transformed by a natural logarithm. All effects were transposed back from the logarithm scale and are reported in absolute terms of change in UAE per unit increase of each explanatory variable. Interaction (effect modification) among the various explanatory variables was finally tested by entering product-terms into the regression equation. A *P*-value of $<$ 0.05 was considered as significant. The comparison between two models with more than one degree of freedom was done by an adjusted Wald test.

Results

Table 1 shows that UAE is higher in men as compared with women. Men have higher levels of all cardiovascular risk factors given in Table 1. Creatinine clearance is also higher in men. The prevalence of microalbuminuria in men is almost double the prevalence in women as shown in the second table. The prevalence of diabetes and hypertension was also higher in men than in women, but women were more often obese. The prevalence of smoking and hypercholesteremia did not differ among the genders. On univariate analysis, as expected higher age, SBP and DBP, BMI, WHR, fasting glucose, cholesterol, and creatinine clearance as well as the use of oral antidiabetic, anti-

Table 1. Population characteristics[a]

	Male n = 4070	Female n = 3771
UAE (mg/24 h)[b]	10.4 (6.8 to 21.1)[c]	8.2 (5.7 to 13.6)[c]
Age (yr)	50 (13)	48 (12)[d]
Systolic BP (mmHg)	134 (18)	124 (21)[d]
Diastolic BP (mmHg)	77 (10)	71 (9)[d]
Body mass index (kg/m^2)	26.3 (3.7)	25.8 (4.7)[d]
Waist-hip ratio[e]	0.94 (0.07)	0.82 (0.08)[d]
Creatinine clearance (ml/min)	112 (27)	95 (23)[d]
Cholesterol (mmol/L)	5.7 (1.1)	5.6 (1.1)[d]
Glucose (mmol/L)	5.0 (1.3)	4.7 (1.1)[d]

[a] Mean (SD).
[b] Median and 25th–75th percentile.
[c] Mann-Whitney test: equal mean rank for both sexes $P < 0.001$.
[d] *t* test null hypotheses: equal means for both sexes $P < 0.001$.
[e] Normal value in women $<$0.8 and in men $<$0.9.

Table 2. Percentage of microalbuminuria and the categorical cardiovascular risk factors

	Male $n = 4070$	Female $n = 3771$
Microalbuminuria	16.4	9.0[a]
Smoking	37.9	37.6
Obesity	14.3	16.3[a]
Diabetes mellitus	4.2	3.1[a]
Hypertension	36.7	25.0[a]
Hypercholesterolemia	26.1	24.8

[a] χ^2 test null hypotheses: distribution is equal among gender $P < 0.05$.

hypertensive, and lipid-lowering therapy were associated with increasing UAE (not shown). Results of the design-based multivariate linear regression analysis are summarized in Table 3. Several predictors demonstrated an independent and additive effect on UAE. A higher UAE was associated with higher age, SBP, DBP, BMI, plasma glucose, and creatinine clearance. Smoking and the use of oral antidiabetic medication were also associated with higher UAE; however, in the multivariate analysis, UAE is no longer explained by plasma cholesterol, WHR, and the use of antihypertensive or lipid-lowering therapy. In the multivariate model, an interaction with gender was found for the following variables: age, BMI, and plasma glucose. Increasing age, BMI, and plasma glucose caused a stronger increase in UAE in male than in female gender. This is illustrated in Figures 1 and 2, which show the relationship between UAE and the tested risk factors in men and women. The tested risk factors are shown as independent variables divided in deciles on the x-axis. For every decile separately, the mean value for the other tested risk factors of that decile was entered into the regression formula to calculate the corresponding UAE on the y-axis. By this graphic representation, Figures 1 and 2 depict the relationship between the risk factors on the x-axis and dependent variable UAE as it occurs in the male and female populations. The figures are created for subjects who do not smoke and who use no antidiabetic medication. For smokers or subjects with antidiabetic medication, the UAE values are 0.5 mg/24 h higher. In Figure 1, which depicts the relationship between UAE and age, BMI, and plasma glucose, the gender interaction is readily apparent. With increasing age, BMI, and plasma glucose, the differences between the mean UAE levels of men and women become larger. These plots not only show the interaction components, but increasing levels of cardiovascular risk factors of the individual point estimates of the explanatory variable, per increasing decile, have also been taken into account. Figure 2 shows the graphs of SBP and DBP and creatinine

Table 3. Design-based multivariate regression model[a]

Lnln UAE as Dependent Variable		$R^2 = 0.2169$			$n = 7841$
	Beta Coefficient	Standard Error	*T* Value	*P* Value	*P* Value Wald Statistic[b]
Gender	−0.939	0.342	−2.74	0.006	
Age	−0.033	0.008	−4.08	<0.001	
Age^2	4.00×10^{-4}	8.19×10^{-5}	4.90	<0.001	
SBP	−0.002	0.003	−0.79	0.427	
SBP^2	2.01×10^{-5}	9.75×10^{-6}	2.06	0.039	
DBP	−0.017	0.005	−3.18	0.002	
DBP^2	1.27×10^{-4}	3.63×10^{-5}	3.51	<0.001	
Creatinine clearance	0.007	0.001	6.75	<0.001	
Creatinine clearance^2	-1.79×10^{-5}	4.45×10^{-6}	−4.03	<0.001	
BMI	−0.077	0.031	−2.46	0.014	
BMI^2	0.002	5.77×10^{-4}	2.84	0.004	
Ln glucose	−1.61	0.465	−3.45	0.001	
Ln glucose^2	0.527	0.135	3.90	<0.001	
Antidiabetic medication	0.104	0.037	2.77	0.006	
Smoking	0.030	0.008	3.91	<0.001	
Gender × age	0.017	0.005	3.25	0.001	
Gender × age^2	-1.86×10^{-4}	5.13×10^{-5}	−3.64	<0.001	<0.001
Gender × BMI	0.022	0.018	1.19	0.233	
Gender × BMI^2	-5.68×10^{-4}	3.30×10^{-4}	−1.72	0.085	<0.001
Gender × ln glucose	0.588	0.293	2.01	0.045	
Gender × ln glucose^2	−0.197	0.086	−2.30	0.022	0.021
Intercept	3.343	0.603	5.54	<0.001	

[a] Reference group of gender is male gender, of smoking is nonsmokers, of antidiabetic medication is non-users. UAE, urinary albumin excretion; SBP, systolic BP; DBP, diastolic BP.
[b] Composite variables tested by adjusted Wald test.

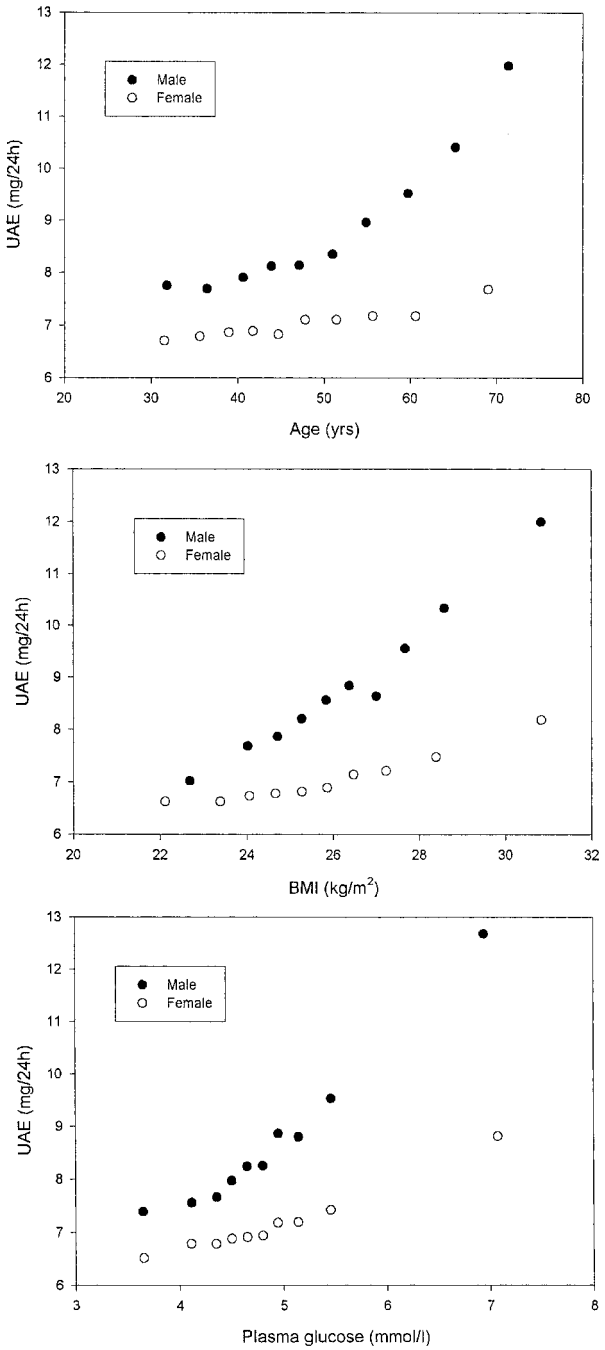

Figure 1. Graphic depiction of the linear regression model showing the interaction of gender with age, body mass index (BMI), and plasma glucose.

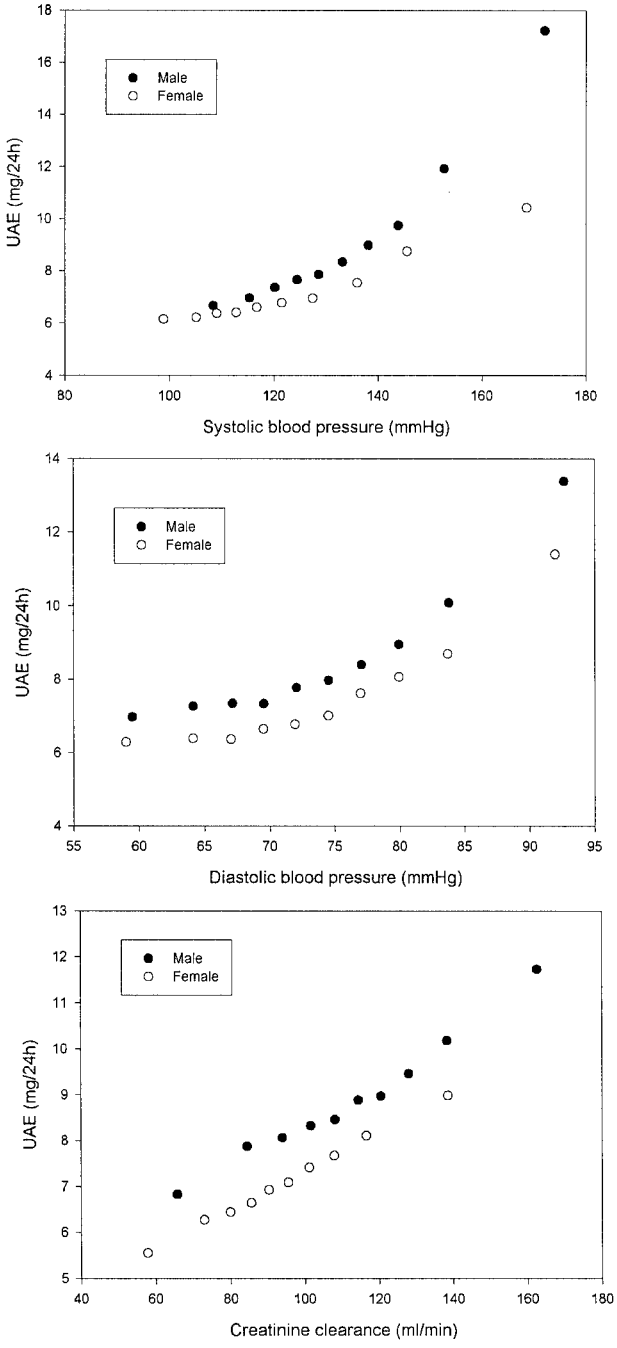

Figure 2. Graphic depiction of the linear regression model showing no interaction of gender with systolic and diastolic BP and creatinine clearance.

clearance *versus* UAE. The curves of men lie on a higher level, but the male and female curves run in parallel, indicating absence of interaction with gender. The presented gender interactions are not influenced by possible interactions with parameters of the metabolic syndrome (BMI, plasma glucose, age). We also studied whether controlling for prevalent cardiovascular diseases modifies either the effect modification or the association between UAE and cardiovascular risk factors. To that purpose, we tested the gender differences in UAE after exclusion of the subjects ($n = 896$) with prior myocardial infarction or cerebrovascular accident and those with peripheral vascular damage (ankle/brachial index < 0.9). Although the significance level of the interaction terms with gender decreased because of a reduction in power, the point estimates of the variables in the model hardly changed, indicating robustness of the primary analyses.

Discussion

In our study, cohort men had a higher prevalence of diabetes and hypertension, but not of obesity, smoking, and hypercholes-

terolemia, than women. The prevalence of microalbuminuria was also higher in men, and the difference compared with women was even more pronounced than for the risk factors itself. The most important finding is that UAE is higher in men than in women for a given level of any single risk factor. In addition in the multivariate model, an interaction with gender was found for age, BMI, and plasma glucose. Thus, for a higher value of age, BMI, and glucose, the differences between the mean UAE levels of men and women become larger. This suggests men to be more susceptible to the detrimental vascular effects of these risk factors.

Our data of a higher UAE in men are in agreement with other studies in the literature. Similarly, others also have shown that men have a higher prevalence of microalbuminuria (11), although Jones *et al.* (13) recently showed a higher prevalence in women. In this study on the NHANES data, albumin/creatinine ratio has been used to determine the presence of microalbuminuria. Creatinine excretion is, however, dependent on muscle mass and therefore on gender; using straightforward creatinine correction independent of gender is therefore not appropriate (14). Our findings that, for each level of a given risk factor, men have a higher UAE than women, and moreover, that this risk increases in men more than in women with increasing age, BMI, and glucose, have not drawn attention yet. Only a few studies examined the gender differences in the association between cardiovascular risk factors and UAE. In the GUBBIO study (15), no gender differences were found in the association between pulse pressure (the difference between SBP and DBP, which indicates vessel stiffness) and microalbuminuria, which is in agreement with our finding of an absence of an interaction of gender with SBP or DBP. However, the multivariate analysis in the GUBBIO study was only adjusted for gender, whereas gender was not studied as effect modifier. In the DESIR study (10) a strong association was found between factors included in the insulin resistance syndrome, that is SBP, plasma glucose, leukocyte count, and hematocrit and microalbuminuria in men. In women, only SBP and triglycerides were significantly associated with microalbuminuria. These results agree with our conclusion that there are gender differences in the impact of cardiovascular risk factors on UAE. In a study in non-diabetic subjects, Gould *et al.* (8) showed that UAE was positively associated with age, BP (SBP and DBP), and fasting plasma glucose and negatively associated with height in men, whereas SBP was the only factor associated with UAE in women. These authors (as well as the DESIR authors) used two different models for studying the difference between genders, while we used one model to determine gender differences. The advantage of our single-model approach is that a direct statistical comparison can be made between men and women. Interaction terms for gender show the variables that are differently associated with UAE. We indeed found positive associations between UAE and age, BP, BMI, and plasma glucose in both genders, but we only observed gender differences in these relations in age, BMI, and plasma glucose. Finally, Metcalf *et al.* (16,17), in their multivariate regression model to predict urinary albumin concentration mentioned the interaction of BMI and gender. Unfortunately, this interaction was not further explored in the results of the multivariate analysis.

Of course, our study has some limitations. The cross-sectional design only allows us to use UAE as a surrogate marker of an increased cardiovascular risk. Thus, on the basis of the present data, we cannot conclude that men have more cardiovascular events than women for a given level of the described cardiovascular risk factors. The prospective follow-up of our subjects, which is ongoing, should be awaited before definite conclusions can be drawn.

We cannot exclude that selection bias has influenced our results. It is possible that we missed certain relations and that the point estimates may be influenced by the selection bias. We do, however, argue that the relations presented are not influenced by a possible selection bias; overall, the responders had comparable cardiovascular risk compared with the nonresponders (data not shown).

Cholesterol did not contribute to UAE in the multivariate model. At the moment, only cholesterol is available as a parameter of the lipid profile. Serum triglyceride and HDL cholesterol would have been a better indication of the cardiovascular risk factor dyslipidemia. In a prospective study of microalbuminuria in type 2 diabetic patients, elevated serum triglyceride and low HDL cholesterol and not cholesterol have been found to predict the rate of progression in microalbuminuria (18).

The strength of our study is that we analyzed UAE in a large sample of the population. Moreover, our data on UAE are based on the measurement of albuminuria in two 24-h urines; similarly, the data on BP are based on the mean of two last measurements of 10 min of BP measuring on two separate occasions.

How could we explain the observed differences in the impact of risk factors on UAE? Differences in gender hormones are assumed to be relevant. It has been argued that women are protected for cardiovascular diseases before menopause by estrogens (19), although data on the protective effect of hormone replacement therapy do not support this assumption. No equivocal protective effect for cardiovascular diseases has been observed of hormone replacement therapy in post-menopausal women (22). Moreover, it was also recently shown that the use of estrogens is in fact associated with a higher instead of a lower risk for microalbuminuria (20,21). This precludes the simply ascription of our present findings to the effects of estrogens in women.

If indeed an increased UAE reflects an increased cardiovascular risk, it can be suggested that each cardiovascular risk factor should be treated more aggressively in men than in women. This holds especially true for a high body mass index and elevated plasma glucose.

We conclude that gender differences exist in the association between cardiovascular and renal risk factors and UAE. At higher ages, BMI, and plasma glucose, men are prone to a more elevated UAE compared with women. These results suggest a possible difference in the mechanism or significance of UAE between both genders. Future studies on UAE should take gender differences into account.

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See related editorial, "Cardiovascular Risk Factors and Urinary Albumin: Vive la Difference," on pages 1415–1416.