An increase or decrease in urinary albumin excretion (UAE) is associated with, respectively, a higher or lower risk for renal and cardiovascular disease, independent of widely known cardiovascular risk factors. This study aimed to identify factors that are associated with changes in UAE in the nondiabetic population using data of the Prevention of Renal and Vascular End stage Disease (PREVEND) Study, a community-based prospective cohort study. Data of the 6647 nondiabetic participants who completed the first (1997 through 2001) and second (2001 through 2003) screening were used. Change in UAE was categorized as regression (n = 650), stable (n = 5240), or progression (n = 757) on the basis of change in class during follow-up, with classes being a UAE <15, 15 to 30, 30 to 300, and >300 mg/24 h. With the use of stepwise forward multinomial regression analysis, changes in BP, fasting glucose concentration, and start of antihypertensive drugs were found to be the most important modifiable variables associated with the risk for progression and regression (P < 0.01 for likelihood ratio test). The odds ratios to develop regression or progression of UAE during follow-up were 0.64 (95% confidence interval [CI] 0.57 to 0.73) and 1.91 (95% CI 1.72 to 2.12), respectively, per 10-mmHg increase in BP during follow-up, 0.89 (95% CI 0.80 to 0.98) and 1.09 (95% CI 1.01 to 1.17), respectively, per 1-mmol/L increase in fasting glucose levels during follow-up, and 1.57 (95% CI 1.21 to 2.06) and 0.70 (95% CI 0.51 to 0.95), respectively, per 0.5 mmol/L increase in UAE during follow-up. In conclusion, changes in glucose concentration and BP and start of antihypertensive drugs are associated with progression and regression of UAE in the nondiabetic population. Although associations do not necessarily suggest causality, it is hypothesized that in the general population, the most important ways to reduce UAE are by lowering glucose concentration and BP (including start of antihypertensive medication), even in normotensive, nondiabetic individuals.
lands that investigated the predictive value of UAE for renal and cardiovascular disease progression. Details of this study have been published elsewhere (22,23). Figure 1 shows the flowchart of the PREVEND Study. The participants of the PREVEND cohort were selected in 1997 from 40,856 individuals who were from the general population and aged between 28 and 75 yr and on the basis of their albumin concentration (UAC) in a morning urine sample. In total 8592 individuals participated in the first screening (1997 through 1998) of the PREVEND study: 6000 individuals with a UAC >10 mg/L and 2592 individuals with a UAC <10 mg/L. After a median follow-up of 4.2 yr (interquartile range 4.0 to 4.5), these individuals were invited for a follow-up survey (2001 through 2003). By then, 240 (217 of whom did not have diabetes) individuals had died and 1458 declined participation. For our study, participants with diabetes (defined according to the criteria of the American Diabetes Association [24]) at baseline were excluded (n = 247), leaving 6647 participants for our study. The PREVEND study was approved by the medical ethics committee of our institution and conducted in accordance with the guidelines of the Declaration of Helsinki. All participants gave written informed consent.

Measurements and Definitions
At baseline and follow-up screening, all participants completed a questionnaire on demographics; renal and cardiovascular disease history; smoking habits; and use of medication for hypertension, hyperlipidemia, or diabetes. For each screening, participants completed two visits at an outpatient unit. During the first visit, height and weight were measured. Before the second visit, two 24-h urine samples were collected after thorough oral and written instructions on the urine collection, and at this visit, a fasting blood sample was drawn. During the first and second visits, BP was measured, in supine position, every minute for 10 and 8 min, respectively, with an automatic device (Dinamap XL Model 9300; Johnson-Johnson Medical, Tampa, FL). Furthermore, information on drug use was collected from community pharmacies.

UAC was determined by nephelometry with a threshold of 2.3 mg/L and intra- and interassay coefficients of variation (CV) of 2.2 and 2.6%, respectively (BNII; Dade Behring Diagnostic, Marburg, Germany). UAE is given as the mean of the two 24-h UAE. High-sensitivity C-reactive protein (hs-CRP) also was determined by nephelometry, with a threshold of 0.175 mg/L and intra- and interassay CV of 4.4 and 5.7%, respectively. Concentrations of cholesterol, glucose, and creatinine were measured in serum using standard methods. Insulin was determined on an Axsym (Abbott, Amstelveen, The Netherlands), with a threshold of 1.0 μU/ml and intra- and interassay CV of 2.6 and 4.3%, respectively. Insulin resistance was estimated using the homeostasis model of assessment of insulin resistance as (fasting insulin [μU/ml] × fasting glucose [mmol/L])/22.5 (25). GFR was estimated (eGFR) with the modified Modification of Diet in Renal Disease (MDRD) formula, taking into account gender, age, race, and serum creatinine concentration (R). Urinary leukocyte and erythrocyte measurements were done by Nephur-test leuco sticks (Boehringer Mannheim, Mannheim, Germany). BP values are given as the mean of the last two recordings of both visits. Mean arterial pressure was calculated as [(2 × diastolic BP) + systolic BP]/3. Participants were considered to use antihypertensive, lipid-lowering, or antidiabetic medication when according to the questionnaire or community pharmacist they took such drugs. Furthermore, we defined use of angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB) separately from other antihypertensive medication using data from the community pharmacies. Participants were considered to smoke when they had smoked in the previous year according to the questionnaire. According to literature, changes in UAE were categorized as progression or regression on the basis of changes in class of UAE during follow-up (10,18,19,26). Although classes of UAE in these studies were defined as

Figure 1. Flowchart of the Prevention of Renal and Vascular End stage Disease (PREVEND) Study.
UAE <30 mg/24 h (normal), UAE 30 to 300 mg/24 h (microalbuminuria), or UAE >300 mg/24 h (macroalbuminuria), there is increasing evidence that levels of UAE <30 mg/24 h already are associated with an increased cardiovascular risk (2,5,27). Therefore, we further subdivided the group with a UAE <30 mg/24 h. For our study, we defined classes of UAE as <15 mg/24 h (low normal), 15 to 30 mg/24 h (high normal), 30 to 300 mg/24 h (microalbuminuria), and >300 mg/24 h (macroalbuminuria).

As an alternative outcome for sensitivity analyses, progression and regression were defined, respectively, as at least doubling (>100%) or halving (<50%) of baseline UAE during follow-up. These cutoff points were calculated on the basis of the 95% confidence interval (CI) of the short-term variation in the UAE measurement (−50%, +100%) in 215 participants of our own population who collected two consecutive 24-h urine samples at baseline and after 3 mo of follow-up. We calculated the ratio of the UAE measured at baseline and 3-mo follow-up. Because ratios have a skewed distribution, we obtained the 95% CI by computing the 95% CI for the log of the mean ratio, after which these values were back-transformed. The cutoff points obtained are similar to values reported in literature (14).

### Statistical Analyses

Analyses were performed using the statistical package SPSS 12.0 (SPSS, Chicago, IL). The level of significance was determined as P < 0.05. For participants with missing data for one or more variables (n = 580, no variable with >5% missing values), data were imputed using expectation maximization as estimation method. Continuous data are reported as mean with SD. In case of a skewed distribution, the median was used instead of the mean as a summary measure. Categorical data are presented as percentages. Differences between groups were tested by one-way ANOVA or a Kruskal-Wallis test in case of skewed distribution. To estimate the incidence of change of UAE class or death during follow-up in the general population, we calculated these percentages using a weight factor that adjusted for the enrichment for UAE at the creation of the PREVEND cohort. These percentages therefore can be extrapolated to the general population.

Variables that were associated with progression or regression of UAE were selected by stepwise forward multinomial regression analysis with change of UAE as outcome variable. Multinomial regression analysis is comparable to logistic regression analysis but allows the outcome variable to have more than two levels, in contrast to the logistic regression analysis that requires the outcome variable to be dichotomous (28). Selection into the model was based on the likelihood ratio test using P < 0.05 as entry criterion and a P > 0.1 as exit criterion. Variables that were entered into the stepwise forward selection procedure were selected from literature and are given in Table 1. However, to prevent problems as a result of possible collinearity between systolic and diastolic BP, we entered only baseline values and follow-up changes of mean arterial pressure as measure of BP into the stepwise forward selection procedure. To adjust for our prescreening selection criterion, being a UAC >10 mg/L (yes/no), we forced this variable into the model selected by the stepwise selection procedure. Furthermore, to adjust for regression to the mean, we forced UAE at baseline into this model. Values for UAE were logarithmically transformed to fulfill the requirement of linearity of the logit. Data of the variables in the final model are presented using the group with stable UAE as the reference group. Odds ratios (OR) and 95% CI are given.

### Results

Table 1 shows the baseline characteristics of the 6647 participants of this study according to levels of UAE at baseline. Participants with a higher UAE at baseline were older; more

| Table 1. Baseline characteristics of the population under study subdivided according to baseline classes of UAEa |
|-------------------------------------------------|-------------------|-------------------|-------------------|-------------------|-------------------|
| Level of UAE (mg/24 h)                        | <15               | 15 to 30          | 30 to 300         | >300              | P                  |
| Age (yr)                                       | 47.3 (11.6)       | 51.0 (12.1)       | 54.5 (11.9)       | 56.1 (12.6)       | <0.001             |
| White (n [%])                                  | 4722 (96.0)       | 884 (95.9)        | 714 (96.7)        | 65 (92.9)         | 0.76               |
| Male (n [%])                                   | 2260 (46.0)       | 516 (56.0)        | 475 (64.4)        | 50 (71.4)         | <0.001             |
| History of myocardial infarction (n [%])       | 197 (4.0)         | 58 (6.3)          | 77 (10.4)         | 11 (15.7)         | <0.001             |
| Smoking (n [%])                                | 1741 (35.4)       | 346 (37.5)        | 305 (41.3)        | 22 (31.4)         | 0.01               |
| BMI (kg/m²)                                    | 25.5 (3.9)        | 26.6 (4.2)        | 27.5 (4.6)        | 28.4 (3.9)        | <0.001             |
| SBP (mmHg)                                     | 124 (16)          | 134 (20)          | 140 (23)          | 149 (23)          | <0.001             |
| DBP (mmHg)                                     | 72 (9)            | 77 (10)           | 79 (11)           | 82 (10)           | <0.001             |
| MAP (mmHg)                                     | 89 (11)           | 96 (13)           | 100 (14)          | 104 (13)          | <0.001             |
| Use of antihypertensive drugs (n [%])          | 545 (11.1)        | 180 (19.5)        | 206 (27.9)        | 22 (31.4)         | <0.001             |
| including use of ACEi/ARB (n [%])             | 150 (3.1)         | 53 (5.7)          | 52 (7.0)          | 6 (8.6)           | <0.001             |
| Cholesterol (mmol/L)                           | 5.6 (1.1)         | 5.7 (1.1)         | 5.9 (1.1)         | 6.1 (1.4)         | <0.001             |
| Use of lipid-lowering drugs (n [%])            | 242 (4.9)         | 57 (6.2)          | 86 (11.7)         | 10 (14.3)         | <0.001             |
| Fasting glucose (mmol/L)                       | 4.7 (0.6)         | 4.9 (0.7)         | 4.9 (0.7)         | 4.8 (0.7)         | <0.001             |
| HOMA-IR (µU/mL per mmol/L)                     | 1.5 (1.2 to 2.3)  | 1.8 (1.2 to 2.9)  | 2.1 (1.3 to 3.3)  | 2.1 (1.3 to 3.6)  | <0.001             |
| hs-CRP (mg/L)                                  | 1.1 (0.5 to 2.4)  | 1.4 (0.6 to 2.9)  | 2.0 (1.0 to 4.2)  | 2.5 (1.2 to 4.8)  | <0.001             |
| eGFR (ml/min per 1.73 m²)                      | 81 (13)           | 81 (14)           | 78 (15)           | 67 (19)           | <0.001             |

aData are means (SD) or medians (interquartile range) in case of skewed data distribution. Statistical analyses were performed with one-way ANOVA or a Kruskal-Wallis test in case of skewed distribution. The χ² test was used in case of categorical variable.
frequently were male; and had increased cardiovascular risk factors such as body mass index (BMI), BP, and cholesterol, which were associated with more frequent use of antihypertensive and lipid-lowering drugs. Furthermore, a higher UAE was associated with higher levels of insulin resistance, but in this nondiabetic population, this was associated with only small differences in fasting glucose. Finally, a higher UAE was associated with higher levels of hs-CRP, a marker of low-grade inflammation.

During a median follow-up of 4.2 yr (interquartile range 4.0 to 4.5), we identified 760 (11.4%) participants as progressors, 652 participants (9.8%) as regressors, and 5235 (78.8%) participants as stable in our cohort. The estimated incidence of progression and regression of UAE and mortality rate according to baseline classes of UAE in the general population are shown in Figure 2. Note that to allow for this generalization to the general population, the percentages given in this figure are adjusted for the enrichment for high UAE in the PREVEND Study. Irrespective of the initial level of UAE, both progression and regression of UAE occur frequently in the nondiabetic population, but in all classes of baseline UAE, there is net progression of UAE. As can be seen, a higher baseline UAE is associated with higher mortality rates, with participants with a baseline UAE between 30 and 300 mg/24 h having a more than four-fold higher mortality during follow-up as participants with a UAE <15 mg/24 h (6.8 versus 1.4%, respectively).

Table 2 shows the baseline characteristics of the total PREVEND population when subdivided according to changes in UAE during follow-up. It is intriguing that compared with the stable group, regressors and progressors had comparable baseline characteristics. Both groups were older when compared with the stable group and had an unfavorable cardiovascular risk pattern, including increased levels of hs-CRP. Compared with the regressor group, progressors more frequently were male and used more antihypertensive and lipid-lowering medication at baseline. Although statistically significant, there were only small differences in baseline eGFR among regressors, progressors, and stable participants.

In Table 3, changes in patient characteristics from baseline to follow-up in the progressor, regressor, and stable group are shown. In contrast to the baseline characteristics, there were important differences between progressors and regressors. In the progressor group, cardiovascular risk factors, including hs-CRP, showed generally a more unfavorable change during follow-up compared with the regressor group, with changes in risk factors in the stable group generally somewhere in between the changes that were seen in the progressor and regressor groups.

Factors that were associated with progression or regression of UAE, as selected by the stepwise forward multinomial regression analysis from the variables given in Tables 1 and 2, are shown in Table 4, including the associated OR. Variables that are not shown in Table 4 were not selected by the stepwise forward selection procedure. The P value of the likelihood ratio test was ≤0.01 for all variables selected, except for eGFR (P = 0.024). Both nonmodifiable demographic factors age and gender were selected into the model. Of the modifiable risk factors at baseline, BP, BMI, and use of lipid-lowering drugs were selected as predictors of changes in UAE. However, all of these variables were significantly associated only with progression of UAE, whereas the 95% CI for the variables indicated a nonsignificant association with regression of UAE (see Table 4).
in case of categorical variables.

Mean arterial pressure; SBP, systolic BP; UAE, urinary albumin excretion; estimated GFR; HOMA-IR, homeostasis model of assessment of insulin resistance; hs-CRP, high-sensitivity C-reactive protein; MAP, mean arterial pressure; SBP, systolic BP; UAE, urinary albumin excretion.

Table 3. Changes in population characteristics according to changes in UAE during follow-upa

<table>
<thead>
<tr>
<th>Table 3. Changes in population characteristics according to changes in UAE during follow-upa</th>
<th>Progression (n = 760)</th>
<th>Stable (n = 5235)</th>
<th>Regression (n = 652)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Δ BMI (kg/m²)</td>
<td>0.8 (1.7)</td>
<td>0.8 (1.7)</td>
<td>0.5 (1.9)b</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Δ SBP (mmHg)</td>
<td>4 (14)b</td>
<td>-2 (11)</td>
<td>-9 (17)b</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Δ DBP (mmHg)</td>
<td>2 (7)b</td>
<td>0 (6)</td>
<td>-4 (9)b</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Δ MAP (mmHg)</td>
<td>2 (9)</td>
<td>-1 (7)</td>
<td>-5 (11)b</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Δ Cholesterol (mmol/L)</td>
<td>-0.2 (1.0)</td>
<td>-0.2 (0.9)</td>
<td>-0.3 (0.8)b</td>
<td>0.002</td>
</tr>
<tr>
<td>Δ Fasting glucose (mmol/L)</td>
<td>0.4 (1.2)b</td>
<td>0.2 (0.9)</td>
<td>0.2 (0.8)</td>
<td>0.02</td>
</tr>
<tr>
<td>Δ hs-CRP (mg/L)</td>
<td>0.7 (6.2)</td>
<td>0.2 (4.9)</td>
<td>-0.9 (6.9)b</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Start of antihypertensive drugs (n [%])</td>
<td>59 (7.8)</td>
<td>430 (8.2)</td>
<td>148 (22.7)b</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Start of ACEi/ARB (n [%])</td>
<td>34 (4.5)</td>
<td>221 (4.2)</td>
<td>93 (14.3)b</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Start of lipid-lowering drugs (n [%])</td>
<td>54 (7.1)b</td>
<td>247 (4.7)</td>
<td>57 (8.7)b</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Start of antidiabetic drugs (n [%])</td>
<td>20 (2.6)b</td>
<td>68 (1.3)</td>
<td>18 (2.8)b</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stop smoking (n [%])</td>
<td>52 (6.8)</td>
<td>376 (7.2)</td>
<td>59 (9.0)</td>
<td>0.20</td>
</tr>
</tbody>
</table>

aData are means (SD) or medians (interquartile range). Statistical analyses were performed with one-way ANOVA or χ² test in case of categorical variables.

bP < 0.01 versus stable (post hoc test).

bP < 0.05 versus stable (post hoc test).

Baseline eGFR and changes in hs-CRP during follow-up that also were selected into the model, the 95% CI indicated a significant association with regression but not with progression of UAE. It should be noted that although the likelihood ratio for the association between changes in hs-CRP and changes in UAE indicated a highly statistically significant relation (P < 0.001), the OR to get progression or regression of UAE for a 1-mg/L change in hs-CRP were low (1.01 and 0.97 for progression and regression, respectively).

In contrast to the other variables, changes in BP and glucose
were associated significantly with both incidence of progression and regression of UAE. An increase of these variables during follow-up was associated with a higher incidence of progression and a lower incidence of regression, whereas a decrease in BP or glucose was associated with a lower incidence of progression and a higher incidence of regression of UAE.

Furthermore, independent of baseline BP and changes in BP during follow-up, the start of antihypertensive medication during follow-up was associated with a lower risk for progression of UAE and increased chance of regression of UAE. Notably, start of ACEi/ARB during follow-up was not selected by the model. When start of ACEi/ARB was added manually to the selected model, the \( P \) value of the likelihood ratio test was 0.07, with the OR for developing progression and regression, being 0.74 (95% CI 0.49 to 1.11) and 1.30 (95% CI 0.92 to 1.84), respectively. Finally, although use of lipid-lowering drugs at baseline was selected into the model, start of lipid-lowering drugs during follow-up was not.

Because our primary definitions of progression and regression are based on changes in class, which may be considered arbitrary, we repeated our analyses using an alternative outcome based on the variation of UAE to define progression (more than doubling in UAE; \( n = 625 \) [9.4%]) and regression (more than halving in UAE; \( n = 541 \) [8.1%]). With the use of this alternative outcome, the stepwise forward multinomial regression procedure selected the same variables as with the primary definition of progression and regression (\( P < 0.01 \) likelihood ratio test, except for eGFR for which \( P = 0.04 \)), except for the use of lipid-lowering drugs at baseline. In addition, baseline levels of glucose, history of myocardial infarction, smoking, and use of antihypertensive medication at baseline were selected into the model.

Because errors in the collection of the 24-h urine samples may have influenced our estimates of 24-h UAE, we repeated our analyses excluding participants with a >20% difference in 24-h creatinine excretion between the first and the second days of urine collection at first and/or second screening (29). This was done on the basis of the assumption that the day-to-day 24-h creatinine excretion is constant. With the use of this exclusion criterion, our model selected the same variables as when the total study population was used, except for baseline eGFR, use of lipid-lowering drugs at baseline, and changes of hs-CRP during follow-up. Furthermore, history of myocardial infarction and start of ACEi/ARB were selected.

Finally, we repeated our analyses using backward elimination in our stepwise multinomial analysis. This procedure selected the same model as the stepwise forward procedure. In addition, however, start of ACEi/ARB remained in the selected model as a result of the \( P \) value of the likelihood ratio test of 0.07, which is below the applied exit criterion of 0.10. Also, we repeated our analyses after excluding participants with leukocyturia or erythrocyturia at baseline or follow-up, which may indicate a urinary tract infection, rendering the measurement of UAE unreliable. Furthermore, we repeated our analyses excluding participants with missing values instead of using imputed data, excluding participants with hypertension at baseline, or excluding participants with impaired fasting glucose at baseline. None of these sensitivity analyses changed the essence of our results. Last, repeating analyses after excluding participants who were using antihypertensive, lipid-lowering, or antidiabetic drugs at baseline and/or follow-up did not essentially change the estimated effects of the other variables in the model.

**Discussion**

We prospectively investigated progression and regression of UAE in the nondiabetic population. The development of UAE
was found to be a dynamic process, with participants frequently showing progression or regression of UAE. This is in line with findings in diabetic populations (10,14,30,31). Factors that were associated with regression or progression of UAE were age, gender, (change in) BP, change in fasting glucose, BMI, eGFR, change in hs-CRP, use of lipid-lowering drugs at baseline, and start of antihypertensive drugs during follow-up. The effects of all factors in the model were independent of the baseline level of UAE. Of the selected variables, only changes in fasting glucose and BP and start of antihypertensive drugs during follow-up significantly affected both progression and regression, indicating that these variables are the most important variables that are associated with changes in UAE.

BP is a widely recognized determinant of UAE in diabetic populations (14,15,32). Our study shows that also in the non-diabetic population, BP is an important factor that is associated with changes in UAE. This furthermore is in line with the finding that hypertensive individuals are at increased risk for development of an increased UAE (33,34). Both a high BP at baseline and a rise in BP during follow-up are associated with an increase for the risk of progression of UAE. Conversely, a decrease of BP during follow-up is associated with more frequent regression of UAE. It is interesting that changes in BP were associated with changes in UAE even with baseline BP added in the same model and after exclusion of participants with hypertension at baseline, indicating that this association was independent of the BP at baseline. Therefore, within ranges of BP that currently are considered (high) normal, increases in BP already are associated with an increase of UAE. This suggests that a decrease in BP levels, even in the normal range, reduces UAE.

Closely related to BP, start of antihypertensive medication was associated with changes in UAE. It is interesting that start of antihypertensive medication was selected even though the model was adjusted for change in BP. This suggests that start of antihypertensive drugs may have a UAE-lowering effect that is unrelated to the simultaneous lowering of BP, as has been suggested of ACEi and ARB (35–37). Notably, >50% of start of antihypertensive drugs was due to start of an ACEi or ARB. Accordingly, there was a strong tendency of ACEi/ARB to be selected into the model. However, a second explanation also is possible. There can be differences between office BP and 24-h BP recordings, with the latter being a better reflection of true BP. Therefore, alternatively, lack of information on 24-h BP levels may explain why start of antihypertensive medication was entered into the model in addition to information on changes of BP.

Similar to BP, glucose concentration is a widely known risk factor for increases in UAE in individuals with diabetes (16,20,24,38). In our study, participants with diabetes were excluded at baseline. It is interesting that we found that in our nondiabetic population, change in fasting glucose concentration was an important factor associated with changes in UAE. This association remained even after exclusion of participants with impaired fasting glucose at baseline. Therefore, as with BP, changes in fasting glucose within ranges of fasting glucose concentration that currently are considered normal are already associated with changes in UAE. This suggests that in individuals with a normal fasting glucose but high UAE, lowering glucose concentrations may reduce UAE.

We also found that use of lipid-lowering drugs was associated with an increased risk for progression of UAE. Because in our study >95% of participants who were on lipid-lowering drugs used a statin, this seems contradictory because use of these drugs reduces the risk for cardiovascular morbidity and mortality (39,40). However, lipid-lowering drugs frequently are prescribed for secondary prevention after myocardial infarction (39) and, thus, to individuals with a high risk for cardiovascular disease progression. Indeed, in our population, 25.1% of users of lipid-lowering drugs had experienced a myocardial infarction versus 3.1% of nonusers of lipid-lowering drugs. Another possible explanation is diminished tubular uptake of albumin as a result of inhibition of hepatic hydroxymethyl glutaryl-CoA in the proximal tubule by statins, leading to an increased UAE (41). Future research needs to be done to study this effect in more detail.

Finally, our results do not allow one to distinguish whether the changes in UAE were associated with intentional or spontaneous changes of the BP and fasting glucose levels during follow-up. Although our findings did not change after exclusion of participants with antihypertensive or anti diabetic drugs at baseline and/or follow-up, nonpharmacologic interventions may have been used to influence these variables. One possible nonpharmacologic intervention may have been weight loss, because changes in weight may induce changes in both BP and fasting glucose levels (42). This would explain why a change in BMI during follow-up was associated univariately with a change in UAE (Table 3) but was not selected into the multinomial regression model. In line with this possibility is the finding that change during follow-up in hs-CRP, which is a marker of subclinical chronic inflammation that is closely associated with generalized vascular endothelial dysfunction and that also can be induced by changes in weight (43), also was selected into the multinomial regression model. Further research is needed to explore the association between changes in UAE and changes in weight.

Strengths of this study are the use of a large, community-based cohort; the use of different definitions of progression and regression of UAE; the use of 24-h urine samples to determine UAE; and the availability of information on time-dependent covariates. Our study has several limitations that need to be mentioned. First, the PREVEND cohort is selected from a mainly white population. Therefore, our results cannot be generalized simply to other populations. Second, the PREVEND cohort is enriched for individuals with increased UAE, which may have influenced our analyses. To adjust for this, we calculated the incidence of progression and regression using a weight factor that corrected for this oversampling. In our multinomial regression models, we adjusted for both baseline UAE and the criterion that was used to select participants into the PREVEND cohort, making it unlikely that the oversampling has influenced our findings substantially. Third, because the UAE is known to show short-term fluctuations that are not due to real progression or regression of UAE, this may have intro-
duced some bias as a result of misclassification in our results. However, such bias will have led to an underestimation of the true association between UAE and associated variables. Therefore, although our study is likely to have identified the most important factors that are associated with changes in UAE, other factors also may be involved in the processes that lead to changes in UAE. Finally, 1698 participants were lost during follow-up, 240 of whom were due to death. The characteristics of participants who were lost to follow-up were comparable with the characteristics of participants who remained in the study, with numerical differences being <3%. However, the difference for UAE was slightly larger, with participants who were lost to follow-up having a higher UAE than participants who remained in the study (median 10.1 versus 9.2 mg/24 h, respectively). Although small, it cannot be excluded that this difference has influenced our results.

Conclusion

Both progression and regression of UAE occur frequently in the nondiabetic population at all levels of UAE. Baseline age, gender, obesity, BP, eGFR, use of lipid-lowering drugs, and changes in hs-CRP were identified as factors that are associated with changes in UAE. Furthermore, changes in BP, start of antihypertensive medication, and changes in fasting glucose concentration were found to be associated with changes in UAE. Although these associations do not need to suggest causality, it is tempting to hypothesize that for the general nondiabetic population, once UAE has increased, the most important ways to reduce UAE are by lowering glucose concentrations and BP (including by start of antihypertensive medication), even in normotensive, nondiabetic individuals. However, future prospective research needs to investigate this issue and assess the effects of lowering UAE in normotensive, nondiabetic individuals on renal and cardiovascular morbidity and mortality.

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Disclosures

None.

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Access to UpToDate on-line is available for additional clinical information at http://www.jasn.org/