Lifestyle changes and kidney function: A 10-year follow-up study in patients with manifest cardiovascular disease

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Abstract

Background: Patients with cardiovascular disease (CVD) are at higher risk of kidney function decline. The current study aimed to examine the association of lifestyle changes with kidney function decline in patients with manifest CVD.

Methods: A total of 2260 patients from the Utrecht Cardiovascular Cohort-Second Manifestations of ARterial disease cohort with manifest CVD who returned for a follow-up visit after a median of 9.9 years were included. The relation between change in lifestyle factors (smoking, alcohol consumption, physical activity and obesity) and change in kidney function (eGFR and uACR) was assessed using linear regression models.

Results: An increase in body mass index (β = 2.81; 95% CI = 3.98; −1.63 per 5 kg/m²) and for men also an increase in waist circumference (β = 0.87; 95% CI = 1.28; −0.47 per 5 cm) were significantly associated with a steeper decline in eGFR over 10 years. Continuing smoking (β = −2.44, 95% CI = −4.33; −0.45) and recent smoking cessation during follow-up (β = −3.27; 95% CI = −5.20; −1.34) were both associated with a steeper eGFR decline compared to patients who remained as non- or previous smokers from baseline. No significant association was observed between physical exercise or alcohol consumption and change in kidney function (eGFR and uACR) was assessed using linear regression models.
CONCLUSIONS: In patients with CVD, continuing smoking, recent smoking cessation and an increase in obesity markers were related to a steeper kidney function decline. Although no definite conclusions from this study can be drawn, the results support the importance of encouraging weight loss and smoking cessation in high-risk patients as a means of slowing down kidney function decline.

KEYWORDS
cardiovascular disease, kidney function decline, lifestyle factors

1 INTRODUCTION
The number of patients with chronic kidney disease (CKD) is increasing worldwide with a current global prevalence in adults of 13%.1 This development is mainly due to the increasing prevalence of lifestyle-related conditions including hypertension and type 2 diabetes (T2D) in combination with increasing life expectancy.2 CKD can progress to end-stage kidney disease (ESKD) and both conditions are associated with decreased life expectancy, loss in quality of life and high healthcare costs.3 Several chronic diseases contribute to an increased risk of CKD, including cardiovascular disease (CVD) which confers a 4-fold increased risk of developing CKD.4 Furthermore, the risk of both ESKD and CVD increases with declining kidney function, and monitoring eGFR decline can predict the time to onset of kidney failure and guide interventions aimed at altering kidney function decline.5

Fortunately, progressive loss of kidney function can be diminished by a number of interventions, including prescription of a RAS-inhibitor,6 SGLT2-inhibitor,7 adequate control of known risk factors such as diabetes mellitus and hypertension, and lifestyle interventions, including smoking cessation,8 weight loss,9 lower alcohol consumption10 and physical exercise.11 Reduced intake of sodium has also been shown to lower kidney function decline.12 These lifestyle factors are especially encouraged in patients with CVD, who often visit the out-patient clinic frequently, and an improvement in almost all risk factors will have a beneficial impact on both CKD and CVD risk. Since patients with CVD are at increased risk of kidney function decline compared to patients without,13 improvement in risk factors including lifestyle changes is likely to have greater benefit in patients with CVD. To the best of our knowledge, no previous study examined the effect of changes in these lifestyle factors on kidney function decline in a high-risk cohort of patients with manifest CVD.

The current study aimed to evaluate the relation between lifestyle changes (change in smoking status, alcohol consumption, markers of obesity and physical exercise) and kidney function decline (assessed by change in eGFR and urine-albumin/creatinine ratio [uACR]) over a 10-year time span in patients with manifest CVD.

2 METHODS

2.1 Study population

The cohort consisted of patients from the Utrecht Cardiovascular Cohort-Second Manifestations of ARTerial disease (UCC-SMART), which is an ongoing prospective cohort study including patients from 18 years of age. The study design and rationale have previously been described in detail.14 Study inclusion for the cohort used for this study occurred between 1996 and 2012. From 2006 onwards, patients with at least 4 years of follow-up were invited once for a second visit with a reassessment of baseline measurements (UCC-SMART 2). Thus, all participants in UCC-SMART 2 had one visit at baseline and a further follow-up visit at least 4 years after the baseline visit. The UCC-SMART study was approved by the local Medical Ethics Committee and written informed consent was obtained from all patients. Reporting of the study conforms to broad EQUATOR guidelines.15

Patients with manifest CVD at baseline who returned for a second measurement and with eGFR levels ≥15 ml/min/1.73 m² at baseline were included (n = 2260). Manifest CVD was defined as cerebrovascular disease, coronary artery disease, symptomatic peripheral artery disease and/or abdominal aortic aneurysm. For specific definitions of CVD see Table S1. After the baseline visit, advice on lifestyle improvements was given according to general clinical practice, and no specific lifestyle intervention was performed in this observational study.

2.2 Collection of data

Data collection at baseline and follow-up visits was identical and acquired using a standardized protocol. eGFR was calculated using the Chronic Kidney Disease Epidemiology
Collaboration (CKD-EPI) formula.\textsuperscript{16} Information on smoking status (never, former or current, including number of pack-years) and alcohol consumption (no alcohol, <1, 1–10, 11–20, 21–30, or >30 units per week) was obtained with a questionnaire. A previously validated questionnaire suitable for ranking subjects\textsuperscript{17} was used for measuring physical activity, with one additional question on the intensity of sports activity. The number of hours per week reported by patients for sports, walking, cycling and gardening was multiplied by a specific metabolic equivalent of task (MET), resulting in several MET hours per week per activity. The total amount of physical activity was the sum of the MET-hours per week for all activities. Visceral adipose tissue (VAT) thickness was measured as the distance between the lumbar spine and the peritoneum, and subcutaneous adipose tissue (SAT) thickness was measured as the distance between the linea alba and the skin. Both were measured using a previously validated ultrasound technique.\textsuperscript{18}

2.3 | Lifestyle changes

Lifestyle factors were assessed at baseline and follow-up regarding smoking, body mass index (BMI), waist circumference, VAT and SAT, physical activity and alcohol consumption. Change in eGFR (ΔeGFR) was calculated by subtracting eGFR at baseline from eGFR at follow-up and dividing the difference by follow-up time in years and multiplying by a factor of 10 to account for change over 10 years (median follow-up time was 10 years). The same approach was done for change in uACR (ΔuACR). Thus, a negative ΔeGFR indicates a fall in eGFR and a positive ΔuACR indicates an increase in uACR over 10 years. The same approach was done for Δpack-years, Δphysical exercise, ΔBMI, Δwaist circumference, ΔVAT and ΔSAT. Changes in smoking status were defined as either smoking cessation at any point during follow-up, smoking start at any point during follow-up, continued smoking or remained as a non-smoker or previous smoker (if the patient had a history of smoking at baseline). Heavy alcohol consumption was defined as >20 units/week for men and >10 units/week for women, and change in alcohol consumption was defined as persistent heavy alcohol consumer, persistent no/light alcohol consumer, stopped heavy alcohol consumption or started heavy alcohol consumption.

2.4 | Registration of events during follow-up

Events were assessed from baseline visit onwards by patients receiving biannual questionnaires obtaining information on incident CVD, bleeding events, diabetes mellitus and end-stage kidney disease. If an affirmative answer was given, additional information from the hospital or general practitioner’s data was gathered. All clinical events were independently evaluated by an endpoint committee consisting of three physicians and conflicting decisions were discussed.

2.5 | Data analyses

Descriptive statistics were assessed by a baseline table and histograms over the distribution of change in eGFR and uACR and change in lifestyle factors between baseline and follow-up. Change in eGFR according to baseline eGFR and baseline age, respectively, was evaluated by plotting mean difference (standard error of the mean [SEM]) stratified according to baseline eGFR and age category.

To account for missing data and avoid potential bias, missing data (eGFR, smoking, pack-years, alcohol consumption and BMI <1%, uACR 3%, physical exercise 27%, waist circumference 6%, VAT 16% and SAT 16%) was imputed using multiple imputations by predicted mean matching (MICE package) with 10 imputation datasets. Results from the imputed datasets were pooled using Rubin’s rule.\textsuperscript{19}

Continuous variables and changes in these were winsorized to the 1st and 99th percentile to diminish the effect of outliers. To investigate the relation between lifestyle changes and kidney function decline over time, linear regression analyses were performed, with ΔeGFR and ΔuACR, respectively, as dependent variables and changes in each lifestyle factor (smoking, alcohol use, physical exercise and markers of obesity) as independent variables. For the categorical independent variables, remaining no/light alcohol consumers and remaining non-smokers, respectively, were set as reference categories. For continuous independent variables, pack-years were assessed per pack-year increase, physical exercise was assessed per 10 METh/week increase, BMI per 5 kg/m\textsuperscript{2} increase, waist circumference and VAT per 5 cm increase and SAT per cm increase.

To account for potential confounding, models were adjusted for baseline eGFR and uACR, respectively, since the change over time might depend on baseline levels. Furthermore, model 1 was adjusted for sex and age, model 2 further for type 2 diabetes status and systolic blood pressure at baseline, and model 3 was further adjusted for BMI, smoking status, alcohol consumption and physical exercise at baseline (if not a determinant of interest). For the main analyses, model 3 was used. The confounders for all models were pre-specified.

Type 2 diabetes status, RASi medication, sex and age were assessed as potential effect modifiers by examining
these as interaction terms with each determinant. Since a significant interaction was found between waist circumference and sex (p-value <.01) and the effect on eGFR decline, the analyses for this determinant were stratified according to sex.

Regarding assumptions of linear regression, linearity between independent variable and outcome, normality of residuals and homoscedasticity were all assessed by visual inspection and no violations were observed. p-values were two-sided, with statistical significance set at .05. All analyses were performed with R-statistic programming (version 4.0.3, R Foundation for Statistical Computing).

2.6 | Sensitivity analyses

To evaluate whether the time since change in smoking status acted as an effect modifier in the relation between change in smoking status and eGFR decline and uACR change, respectively, an interaction term between change in smoking status and time since smoking status was added to the models. Exploratory models were evaluated with the addition of blood pressure-lowering medication, lipid-lowering medication as well as education level at baseline added to model 3. Since it has been substantially debated whether to adjust for baseline variables in regression models using change as a dependent variable, we also performed the analyses without adjusting for baseline variables for eGFR and uACR, respectively, and the results did not change substantially (data not shown). Furthermore, due to the difference in follow-up between patients, we performed the analyses for the categorical determinants (change in smoking status and change in alcohol intake) adjusted for follow-up time as a confounder. Baseline characteristics for patients in SMART2 (thus patients who returned for a follow-up visit) vs patients in SMART1 (who did not return for a follow-up visit) are shown in Table S2.

3 | RESULTS

3.1 | Baseline characteristics

A total of 2260 patients with clinically manifest CVD were included in the study. The mean age at visit 1 was 58 years and the majority were men (78%). Median follow-up (time between first and follow-up visit) was 9.9 years (IQR 8.7–10.8, range 2.9–16.8 years). Patient characteristics for both visits are shown in Table 1. Median eGFR was 79.3 ml/min/1.73 m² (IQR 68.4–90.0) at baseline and 77.0 ml/min/1.73 m² (IQR 64.7–87.7) at follow-up, and 61% of patients experienced an unfavourable change in eGFR over 10 years (Figure 1A). Median uACR was 0.82 mg/mmol (IQR 0.47–1.63) at baseline and 0.96 mg/mmol (IQR 0.59–1.75) at follow-up, and 56% of patients experienced an unfavourable change in uACR over 10 years (Figure 1B).

Overall mean eGFR decline over 10 years was 5.0 ml/min/1.73 m² (SEM 0.26) and the overall mean uACR increase was 0.04 mg/mmol (SEM 0.6). A steeper eGFR decline was observed in patients with normal kidney function at baseline (>90 ml/min/1.73 m²) and in patients with CKD 3b or higher at baseline (p-value <.01) (Figure 2A). Patients with higher baseline age also had steeper eGFR decline, especially patients ≥70 years (p-value <.01) (Figure 2B). Change in lifestyle factors between baseline and follow-up is shown in Figure 3.

3.2 | Relation between change in smoking status and kidney function decline

Mean 10-year eGFR decrease for patients who remained non- or previous smokers was 4.3 ml/min/1.73 m² (SEM 0.3) (reference category). When adjusting for sex, age, eGFR, type 2 diabetes status, systolic blood pressure, alcohol consumption, exercise and BMI at baseline, patients who continued smoking (n = 319) had a significant additional eGFR decline compared to patients who remained non- or previous smoker of 2.44 ml/min/1.73 m² over 10 years (β = −2.44; 95% CI −4.43, −0.45) (Figure 4). Patients who stopped smoking during follow-up (n = 333) also had a significantly steeper decrease in eGFR of 3.27 ml/min/1.73 m² over 10 years compared to patients who remained non- or previous smokers (β = −3.27; 95% CI −5.20, −1.34). The same trend was seen in patients who started smoking during follow-up (n = 59) (β = −2.82; 95% CI −7.08, 1.43), although this relationship was not significant. Per 1 unit increase in pack-years, eGFR decline was 0.10 steeper (β = −0.10; 95% CI −0.17, −0.04). The results were not substantially different when only adjusting for sex and age or when adjusting for the aforementioned confounders excluding lifestyle factors (Table S3). Concerning the change in smoking status and change in uACR, no significant relation was seen, although a trend of continuing smoking or starting smoking and an increase in uACR was observed (Figure 5).

3.3 | Relation between change in markers of obesity and kidney function decline

Regarding measures of obesity, the effect of change in waist circumference on change in eGFR was different for
men and women. The overall mean change in BMI over 10 years was 0.8 kg/m² (SEM 0.02). The overall mean change in waist circumference was 4.4 cm (SEM 1.1) for men and 5.6 cm (SEM 1.0) for women. For VAT and SAT, the overall mean change was 0.2 cm (SEM 0.08) and −0.2 cm (SEM 0.04), respectively. Per 5 units increase in BMI, eGFR decline steepened with 2.81 ml/min/1.73 m² (β = −2.81; 95% CI −3.98, −1.63). Per 5 cm increase in waist circumference, eGFR decline for men was 0.87 ml/min/1.73 m² steeper (β = −0.87; 95% CI −1.28, −0.47) (Figure 4). No significant relation was observed between change in waist circumference and eGFR decline in men and women. The overall mean change in BMI over 10 years was 0.8 kg/m² (SEM 0.02). The overall mean change in waist circumference was 4.4 cm (SEM 1.1) for men and 5.6 cm (SEM 1.0) for women. For VAT and SAT, the overall mean change was 0.2 cm (SEM 0.08) and −0.2 cm (SEM 0.04), respectively. Per 5 units increase in

| TABLE 1 Baseline table |
|-------------------------|
| n = 2260 | Baseline | Follow-up |
| Sex (male) | 1752 (78%) | 1752 (78%) |
| Age (years) | 58 ± 9 | 66 ± 9 |
| History of cerebrovascular disease | 589 (26%) | 640 (28%) |
| History of coronary artery disease | 1453 (64%) | 1540 (68%) |
| History of peripheral artery disease | 355 (16%) | 418 (19%) |
| History of abdominal aortic aneurism | 119 (5%) | 161 (7%) |
| Type 2 diabetes | 287 (13%) | 494 (22%) |
| Metabolic syndromea | 1097 (49%) | 1233 (55%) |
| Smoking | 653 (29%) | 377 (17%) |
| Packyears | 19 ± 19 | 23 ± 21 |
| Alcohol use (>10 units for women and >20 units for men) | 312 (14%) | 224 (10%) |
| Physical exercise (MET hours/week) | 53 ± 39 | 53 ± 38 |
| Education level | | |
| Low | 1040 (46%) | 974 (43%) |
| Middle | 598 (26%) | 629 (28%) |
| High | 622 (28%) | 657 (29%) |
| Blood-pressure lowering medication | 1665 (74%) | 1812 (80%) |
| Lipid lowering medication | 1541 (68%) | 1944 (86%) |
| Anti-platelet therapy | 1875 (83%) | 2078 (92%) |
| RASi medication | 757 (34%) | 1247 (55%) |
| Body mass index (kg/m²) | 27 ± 4 | 27 ± 4 |
| Waist circumference (cm) | 95 ± 11 | 99 ± 12 |
| Systolic blood pressure (mmHg) | 139 ± 20 | 139 ± 17 |
| Diastolic blood pressure (mmHg) | 82 ± 11 | 79 ± 10 |
| eGFR (ml/min/1.73 m²)b | 79 (68–90) | 77 (65–88) |
| u-Albumine/creatinine ratio (mg/mmol) | 0.82 (0.47–1.63) | 0.96 (0.59–1.75) |
| Cholesterol (mmol/L) | 4.9 ± 1.2 | 4.5 ± 1.1 |
| Triglycerides (mmol/L) | 1.4 (1.0–2.0) | 1.3 (0.9–1.8) |
| HDL cholesterol (mmol/L) | 1.2 ± 0.4 | 1.3 ± 0.4 |
| LDL cholesterol (mmol/L) | 2.9 ± 1.0 | 2.6 ± 0.9 |
| Microalbuminuria | 188 (8%) | 268 (12%) |
| Macroalbuminuria | 23 (1%) | 30 (1%) |
| Visceral adipose tissue thickness (cm) | 9.0 ± 2.5 | 9.3 ± 2.6 |
| Subcutaneous adipose tissue thickness (cm) | 2.5 ± 1.3 | 2.3 ± 1.1 |

Note: Median time between visits was 9.9 years (IQR 8.7–10.8 years). Data are mean ± SD for normally distributed variables or median (interquartile range) for skewed distributions. Categorical variables are presented as numbers (%).

a Metabolic syndrome was defined according to the National Cholesterol Education Program Adult Treatment Panel III definition.

b eGFR was estimated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula.
women, and also overall no significant relation was observed between 10-year change in VAT or SAT and eGFR decline. Adjusting for only sex and age or the aforementioned confounders excluding lifestyle factors did not significantly alter the results (Table S3). No significant relation was observed between changes in markers of obesity and change in uACR (Figure 5).

3.4 | Relation between change in physical exercise and kidney function decline

The mean 10-year change in physical activity was $-1.8$ METh/week (SEM 10.2). No significant relation was observed between change in physical exercise and eGFR decline ($\beta = 0.09; 95\%$ CI $-0.13, 0.31$) or change in uACR ($\beta = -0.06; 95\%$ CI $-0.14, 0.01$).

3.5 | Relation between change in alcohol consumption and kidney function decline

Mean 10-year eGFR decline in patients who remained no/light alcohol consumers was $4.9$ ml/min/1.73 m$^2$ (SEM 0.25). No significant relation was observed between continuing, starting or stopping heavy alcohol consumption and eGFR decline compared to patients who remained no/light alcohol consumers. Adjusting for fewer confounders did not significantly change the results. No significant
relation was observed between change in alcohol consumption and change in uACR.

3.6 | Sensitivity analyses

The results did not change substantially when adding lipid-lowering medication, blood pressure-lowering medication and education level to model 3 (Tables S3 and S4). Furthermore, no indication of an interaction between smoking status and time since the smoking status was found (p-value .11 for eGFR decline and 0.42 for change in uACR). Also, no interaction was observed between type 2 diabetes, or age, respectively, and eGFR decline or uACR change. No interaction between RASi medication use at baseline and eGFR decline or uACR change was observed. When performing the analyses for change in smoking status and change in alcohol intake adjusted for follow-up time, the results did not change significantly (data not shown).

4 | DISCUSSION

The current study found that in a population of patients with manifest vascular disease, the majority of patients improved in lifestyle factors regarding smoking and alcohol consumption, however, markers of obesity worsened over a 10-year follow-up period. A steeper eGFR decline over 10 years was observed for patients who continued smoking or recently stopped smoking during follow-up compared to patients who remained non- or previous smokers. Also, an increase in BMI, and for men increase in waist circumference, was associated with a steeper eGFR decline over 10 years.

Continuing smoking and recent smoking cessation compared to continuing as non- or previous smokers were associated with accelerated eGFR decline in the present study. Also, a negative trend regarding eGFR decline was observed in patients who started smoking compared to patients who continued being non- or previous smokers. These findings are in line with several previous studies that found an increased risk of CKD in current or former smokers compared to non-smokers. The pathophysiology behind smoking aggravating kidney function decline is caused by several underlying mechanisms, including renovascular disease due to endothelial cell injury. It is also worth noting that smoking cessation occurred at an unknown time between baseline and follow-up and could be very recent, which possibly explains the accelerated eGFR decline observed in the group who stopped smoking.
The current study found an increase over 10 years in BMI to be associated with a steeper eGFR decline in patients with CVD. Furthermore, an increase in waist circumference was associated with a steeper eGFR decline in men with CVD, however, this association was attenuated in women. Previous studies have found higher baseline BMI to be associated with an increased risk of CKD. The exact reason for the differences found in men and women is not fully understood, although this observation was also observed in previous studies. It is well known that men have a faster decline in kidney function compared to women, and these findings have been stipulated as due to the protective effects of endogenous estrogens in women. Possibly, several of the biological mechanisms attributed to the relationship between obesity and kidney disease are also affected by sex hormones, explaining sex as an effect modifier in the relation between waist circumference and accelerated eGFR decline. Furthermore, creatinine depends on muscle tissue, and with an increase in obesity markers, muscle mass also increases, resulting in an increase in creatinine and thus lower eGFR. This might cause some overestimation in the relation between the increase in obesity markers and eGFR decline observed in this study.

Change in physical activity in our study was not associated with kidney function decline in patients with manifest CVD. Previous studies have found higher physical activity to be associated with decreased risk of rapid eGFR decline. Physical inactivity indirectly influences the risk of CKD through the development of obesity, diabetes and hypertension, which were all adjusted for in our main analyses. Also, serum creatinine concentrations and muscle mass are in general higher in active people than in sedentary people, which could disguise the beneficial effects of an increase in physical activity on kidney function decline.

Counterintuitively, the current study found a trend towards a less steep eGFR decline in patients who continued or started heavy alcohol consumption (>10 units per week for women and >20 units per week for men) compared to patients who remained no/light alcohol consumers, however not significant. It is well known that alcohol consumption has severe detrimental effects on overall health and mortality, including CVD. Previous studies

| Change in lifestyle factor | No. of patients (%) | β (95%CI) |
|---------------------------|---------------------|-----------|
| **Smoking**               |                     |           |
| Continued as non- or previous smoker | 1549 (69%) | Ref |
| Continued smoking         | 319 (14%)           | -2.44 (-4.43 ; -0.45) |
| Stopped smoking           | 333 (15%)           | -3.27 (-5.20 ; -1.34) |
| Started smoking           | 59 (3%)             | -2.82 (-7.08 ; 1.43) |
| Packyears (per packyear increase) | 2260 | -0.10 (-0.17 ; -0.04) |
| **Physical exercise**     |                     |           |
| Physical activity (per 10 MET hours/week increase) | 2260 | 0.09 (-0.13 ; 0.31) |
| **Obesity**               |                     |           |
| Body mass index (per 5 kg/m2 increase) | 2260 | -2.81 (-3.98 ; -1.63) |
| Waist circumference (per 5 cm increase) |
| Men                       | 1752 (78%)          | -0.87 (-1.28 ; -0.47) |
| Women                     | 508 (22%)           | 0.22 (-0.43 ; 0.87) |
| Visceral adipose tissue (per 5 cm increase) | 2260 | -0.53 (-3.47 ; 2.41) |
| Subcutaneous adipose tissue (per cm increase) | 2260 | -0.74 (-1.90 ; 0.41) |
| **Alcohol**               |                     |           |
| Continued no/light alcohol consumption | 1862 (82%) | Ref |
| Continued heavy alcohol consumption | 142 (6%)  | 2.54 (-0.17 ; 5.25) |
| Started heavy alcohol consumption | 83 (4%)   | 1.81 (-1.66 ; 5.29) |
| Stopped heavy alcohol consumption | 173 (8%) | -2.00 (-4.47 ; 0.47) |

**FIGURE 4** Relation between change in lifestyle factors and eGFR decline over 10 years. Adjusted for sex, age, type 2 diabetes status, systolic blood pressure, smoking status, number of alcohol units per week, exercise and body mass index at baseline (if not a determinant of interest) and eGFR at baseline and stratified according to sex for waist circumference as a determinant.
examining alcohol consumption and kidney function decline have shown controversial results, and some studies indicated a possible inverse association. However, the findings in our study are most likely due to epidemiologic fallacies playing a role in the inverse relationship between change in alcohol consumption on kidney function decline. Since patients who have a more rapid eGFR decline often have several comorbidities, they might be less prone to continue or start heavy alcohol consumption, and the trend found in this study might thus partly be due to reverse causality. Furthermore, very few people started (4%) or continued (6%) heavy alcohol consumption, reducing the power of finding an effect in these groups.

The strengths of the current study include a large study population of patients with manifest CVD at baseline and the repeated and complete measurement of lifestyle factors and eGFR and uACR concentrations over substantial follow-up time. Also, as demonstrated by the high prevalence of preventive drug prescriptions, the cohort is very contemporary. Furthermore, the cohort consists of patients with a broad spectrum of vascular diseases, making the results widely applicable to other patients with vascular diseases. Potential limitations also need consideration. eGFR was used as an estimate for kidney function, however, some determinants may have inherent effects on eGFR not associated with kidney function, why the causal relations should be interpreted with this in mind. Patients were assessed at baseline and follow-up, which might not be fully representative of the follow-up period. For example, it could have been that some patients quit and restarted smoking, heavy alcohol consumption or certain medication, which would then not have been reflected in the follow-up data. Furthermore, the standardized questionnaires regarding smoking and alcohol intake were not specifically validated for lifestyle habits. Also, social desirability bias and recall bias could have influenced the answers concerning physical activity, smoking and alcohol consumption, potentially leading to an underestimation of these relations with kidney function decline. As with all etiologic studies, unmeasured confounding might be present, for example, social class, although the relations did not change when further adjusting for the level of education. Furthermore, patients eligible for the study had to return for a follow-up visit approximately 10 years after

| Change in lifestyle factor | No. of patients (%) | β (95%CI) |
|---------------------------|---------------------|-----------|
| Smoking                   |                     |           |
| Continued as non- or previous smoker | 1549 (69%)         | Ref       |
| Continued smoking         | 319 (14%)           | 1.05 (0.10; 2.01) |
| Stopped smoking           | 333 (15%)           | 0.12 (-0.79; 1.02) |
| Started smoking           | 59 (3%)             | 0.47 (-1.39; 2.33) |
| Packyears (per packyear increase) | 2260              | -0.01 (-0.04; 0.02) |
| Physical exercise         |                     |           |
| Physical activity (per 10 MET hours/week increase) | 2260              | -0.06 (-0.14; 0.01) |
| Obesity                   |                     |           |
| Body mass index (per 5 kg/m2 increase) | 2260            | 0.04 (-0.53; 0.61) |
| Waist circumference (per 5 cm increase) | 2260             | -0.03 (-0.22; 0.16) |
| Visceral adipose tissue (per 5 cm increase) | 2260            | 0.29 (-0.70; 1.27) |
| Subcutaneous adipose tissue (per cm increase) | 2260           | -0.05 (-0.30; 0.20) |
| Alcohol                   |                     |           |
| Continued no/light alcohol consumption | 1862 (82%)    | Ref       |
| Continued heavy alcohol consumption | 142 (6%)       | -0.14 (-1.41; 1.13) |
| Started heavy alcohol consumption | 83 (4%)        | 1.00 (-0.59; 2.60) |
| Stopped heavy alcohol consumption | 173 (8%)      | -0.52 (-1.83; 0.79) |

FIGURE 5 Relation between change in lifestyle factors and change in uACR over 10 years. Adjusted for sex, age, type 2 diabetes status, systolic blood pressure, smoking status, number of alcohol units per week, exercise and body mass index at baseline (if not a determinant of interest) and uACR at baseline.
the first visit, possibly resulting in selection bias. However, one would expect this to also result in underestimation of the relations between healthy lifestyle changes and kidney function decline, as the healthier subjects, and thus subjects with a less steep eGFR decline would return for a follow-up visit. In the current study, the duration of RASi usage before baseline or time of initiation or cessation of RASi during follow-up was not known, and since initiation of a RASI is potentially associated with an acute decrease in eGFR, this could potentially have an effect on eGFR change. However, in the current study, treatment with a RASI was not shown to be an effect modifier in the relationship between any lifestyle factor and eGFR decline. Also, very few patients in the cohort started in the relationship between any lifestyle factor and eGFR decline. Although no definite conclusions from this study can be drawn, the results support the importance of encouraging weight loss and smoking cessation in high-risk patients as a means of slowing down kidney function decline.

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CONFLICT OF INTEREST
On behalf of all authors, the corresponding author states that there is no conflict of interest.

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