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CLINICAL RESEARCH

Determinants of the Evolution of Kidney Function With Age

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Introduction: Kidney function declines with age, but its determinants in the general population remain incompletely understood. We investigated the rate and determinants of kidney function decline in the general population.

Methods: Participants with information on kidney function were selected from a population-based cohort study. Joint models were used to investigate the evolution of the estimated glomerular filtration rate (eGFR, expressed in ml/min per 1.73 m^2 per year) and the urine albumin-to-creatinine ratio (ACR, expressed in mg/g per year) with age. We stratified for 8 potential determinants of kidney function decline, including sex, cardiovascular risk factors, and cardiovascular disease.

Results: We included 12,062 participants with 85,922 eGFR assessments (mean age 67.0 years, 58.7% women) and 3522 participants with 5995 ACR measurements. The annual eGFR decline was 0.82 and the ACR increase was 0.05. All determinants appeared detrimental for eGFR and ACR, except for prediabetes and higher body mass index which proved only detrimental for ACR. In participants without the determinants, eGFR decline was 0.75 and ACR increase was 0.002. Higher baseline eGFR but faster eGFR decline with age was detected in men (0.92 vs. 0.75), smokers (0.90 vs. 0.75), and participants with diabetes (1.07 vs. 0.78).

Conclusion: We identify prediabetes, smoking, and blood pressure as modifiable risk factors for kidney function decline. As with diabetes, hyperfiltration seems important in accelerated kidney function decline in men and smokers. The interpretation of kidney function decline may require adjustment for age and sex to prevent overdiagnosis of chronic kidney disease in aging populations.

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Aging is one of the most important risk factors for chronic diseases,[1] caused by its negative impact on the structure and function of several organs in the human body[2,3] and most notably on the kidney.[3] Currently, estimated glomerular filtration rate (eGFR) is the most widely used measure of kidney function.[4] The eGFR will gradually decrease with the aging of the kidney, although the exact age at which the decline starts is not clearly defined.[2,5–7] The decrease is probably caused by an increase in nephrosclerosis combined with nephron loss.[8,9] More specifically, it has been shown that healthy adults lose approximately 48% of their nephrons from the age of 18 to 29 years to the age of 70 to 75 years.[8] Knowledge on this age-related kidney function decline is important, as decreased kidney function, whether or not physiological, has been associated with increased mortality.[10–13] In addition, distinguishing physiological from pathophysiological kidney function decline is pivotal in preventing overdiagnosis of chronic kidney disease (CKD), especially in aging populations.

The decline in eGFR with age can be accelerated by several factors, such as hypertension,[14–16] smoking,[14,16] and obesity.[16–18] Overall, a decline in GFR at approximately 8 ml/min per 1.73 m^2 per decade probably starting between the ages of 30 and 40 years[2,7,19,20] is considered as the average kidney function decline. However, previous literature has reported substantial variability in average annual eGFR decline ranging from 0.3 to 2.6 ml/min per 1.73 m^2.[21–29] This variability may be explained by differences in study design and

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population, in the method used to evaluate eGFR, the number of available eGFR assessments, and in the statistical methodology.

To study and quantify the decline in kidney function with age, prospective longitudinal studies with multiple assessments of eGFR carried out within the general population are required. One of the limitations of previous longitudinal studies is that they do not account for the possible occurrence of nonrandom dropout. Therefore, we aimed to study the decline in kidney function with age determined by eGFR and the urine albumin-to-creatinine ratio (ACR) using joint modeling, which models the longitudinal measurements and dropout process together to avoid bias introduced by nonrandom dropout.[30,31] Kidney function decline could depend on several characteristics which can be taken into account with the goal of personalized medicine. In addition, determining specific rates of kidney function decline for certain subgroups has the potential to improve prediction and prevention of accelerated kidney function decline. Therefore, we also aimed to study the decline in kidney function with age in subgroups with or without potential determinants.

METHODS

Study Design, Setting, and Population

The current study was embedded in the Rotterdam Study, an ongoing prospective population-based cohort study. The design and rationale of the Rotterdam Study have been described in detail elsewhere.[32] Participants from the Rotterdam Study were eligible for the study if they had at least 1 measurement of the eGFR calculated from serum creatinine in the Rotterdam Study or the Star-MDC database, a general practitioner database, available. A more detailed description of the methods can be found in the Supplementary Material.

Assessment of Kidney Function and Covariates

Kidney function was measured within the Rotterdam Study as well as obtained through the Star-MDC database. All serum creatinine measurements were performed using an enzymatic assay method, and eGFR was calculated according to the CKD Epidemiology Collaboration equation.[33] Urine albumin and creatinine were determined by a turbidimetric method and enzymatic method, respectively. The ACR was estimated by dividing urine albumin by urine creatinine (mg/g). Information on data collection of other covariates can be found in the Supplementary Material.

Assessment of Kidney Replacement Therapy and Mortality

Information on kidney replacement therapy was obtained through linkage with the Renine database which contains data of patients on chronic kidney replacement therapy. Information on vital status of all participants from the Rotterdam Study is continuously obtained from the central registry of the municipality in Rotterdam and through linkage with records from the general practitioners in the study area. Follow-up for all-cause mortality was completed until May, 2018. Follow-up time for all participants was calculated from the date of the first eGFR assessment available in the Rotterdam Study or the Star-MDC database until the date of receiving their first kidney replacement therapy, date of death, or the end of the study period (May, 2018), whichever came first.

Statistical Analysis

We investigated the evolution of kidney function (eGFR and ACR) with age using joint models. In the current study, the longitudinal submodel is defined as a linear mixed model describing the longitudinal profiles of kidney function with age. Age is used as the time variable and defined as the age of the participant at the time of the kidney function measurement. Potential left truncation was taken into account in the analyses. To check for potential nonlinearity in the longitudinal profiles of eGFR, we fitted natural cubic splines of age with 3 knots and boundary knots set at the 5th and 95th percentiles. The random-effects part of the model included the linear effect of age. The survival submodel is defined as a Cox-proportional hazards model, accounting for left truncation. The event variable is defined as a combination of first kidney replacement therapy and death, as both are responsible for dropout of the study participants. Because measures of the ACR were not normally distributed, they were natural log-transformed in all analyses. Rates of ACR change were predicted from the final models including the log-transformed ACR and back-transformed for interpretability. Rates for both eGFR and ACR change were reported per year increase in age.

Predefined stratification analyses by sex and baseline body mass index (BMI), smoking, history of cardiovascular disease (CVD), systolic blood pressure (SBP), hypertension, prediabetes, and diabetes were conducted to study possible determinants of the decline in kidney function with age. To investigate the role of blood pressure (BP)-lowering medication, we further stratified the 4 groups of SBP by BP-lowering medication use. For the analysis of prediabetes, prevalent cases of diabetes were excluded. In addition, stratification on BMI, smoking, history of CVD, SBP, hypertension, prediabetes, and diabetes was also performed in men and women separately for eGFR only. Furthermore, to study on how much of the variation in

the urine ACR can be explained by muscle mass, we calculated the explained variability of the urine ACR for the skeletal muscle index in a cross-sectional analysis.

RESULTS

Baseline Characteristics

Of the 14,926 participants of the Rotterdam Study, we excluded those without informed consent ($n = 313$), those without eGFR assessments in the Rotterdam Study or the Star-MDC database ($n = 871$), and those with only eGFR assessments before the start ($n = 1657$) or after the end ($n = 23$) of follow-up, leaving 12,062 participants in the final study population (Supplementary Figure S1). Mean age of the total study population at baseline was 67.0, with a standard deviation (SD) of 10.7 years, and 58.7% were women (Table 1). The total number of repeated eGFR assessments was 85,922, including 17,908 assessments from the Rotterdam Study and 68,014 from the Star-MDC database (median of 5 assessments per participant). During a median follow-up of 9.6 years (interquartile range 7.0–15.2 years), 5250 deaths occurred and 36 participants started kidney replacement therapy.

Table 1. Baseline characteristics of the study population

Characteristics	Total population ($n = 12,062$)
Age, yr ($n = 12,062$)	67.0 ± 10.7
Women, sex, *n* (%) ($n = 12,062$)	7077 (58.7)
Educational level ($n = 11,923$)	
Primary education, *n* (%)	1770 (14.8)
Lower/intermediate general and lower vocational education, *n* (%)	4896 (41.1)
Higher general and intermediate vocational education, *n* (%)	3310 (27.8)
Higher vocational education and university, *n* (%)	1947 (16.3)
BMI, kg/m^2 ($n = 9829$)	27.2 ± 4.2
Smoking, *n* (valid %) ($n = 10,052$)	
Never	3293 (32.8)
Past	4802 (47.8)
Current	1957 (19.5)
Alcohol, g/d (n = 8272)	9.3 ± 12.5
eGFR creatinine, ml/min per 1.73 m^2 ($n = 12,062$)	77.2 ± 16.5
Urine albumin/creatinine ratio, mg/g ($n = 3092$)[a]	3.5 (2.2–6.3)
Serum cholesterol, mmol/l ($n = 9871$)	5.7 ± 1.0
Serum triglyceride, mmol/l ($n = 9902$)	1.5 ± 0.8
Systolic blood pressure, mm Hg ($n = 9927$)	140 ± 21
Diastolic blood pressure, mm Hg ($n = 9927$)	79 ± 12
Hypertension, *n* (valid %) ($n = 9730$)	6250 (63.1)
Diabetes, *n* (valid %) ($n = 10,337$)	1246 (12.1)
Prediabetes, *n* (valid %) ($n = 10,766$)	1955 (18.2)
History of CVD, *n* (valid %) ($n = 10,286$)	865 (8.4)

BMI, body mass index; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; n, number.
[a]Total population with at least 1 measurement of the urine albumin-creatinine ratio; $n = 3522$.
Data are presented as number (%), number (valid %), median (interquartile range) or mean ± SD. Values are found for nonimputed data. For variables with missing data, valid % is given.

Age-Related Decline in eGFR and Sex Differences

The decline of eGFR with age was 0.82 ml/min per 1.73 m^2 per year increase in age ($P < 0.001$; Figure 1). When we stratified by potential determinants of kidney function decline, differences in the longitudinal evolution of kidney function were revealed for all determinants except for BMI and prediabetes (Figure 2). At younger age, eGFR of men was higher compared with eGFR of women. However, lines crossed at the age of 75 years, after which a faster decline in eGFR was present in men compared with women. Overall, the decline of eGFR with age in men was 0.92 ml/min per 1.73 m^2 compared with 0.75 ml/min per 1.73 m^2 in women (Supplementary Table S1).

Other Determinants of eGFR Decline

Stratification by smoking status revealed a higher eGFR for current smokers at younger age, but the eGFR of this group became similar to the eGFR of never and past smokers with increasing age. The decline of eGFR with age was 0.90 ml/min per 1.73 m^2 in current smokers compared with 0.75 and 0.82 ml/min per 1.73 m^2 in never and past smokers, respectively (Supplementary Table S1). Participants with diabetes had higher baseline levels of eGFR; however, a faster decline with age was seen in this group compared with participants without diabetes and lines crossed at the age of 72 years. Overall, the decline of eGFR with age was 1.07 ml/min per 1.73 m^2 in participants with diabetes and 0.78 ml/min per 1.73 m^2 in participants without diabetes. Participants with a history of CVD and those with hypertension had a faster decline in eGFR with age compared with those without CVD or hypertension (decline 0.90 vs. 0.80 ml/min per 1.73 m^2 in participants with and without CVD, respectively; annual 0.88 vs. 0.65 ml/min per 1.73 m^2 in participants with and without hypertension, respectively). When analyzing the 4 groups determined by SBP, participants with SBP ≥140 mm Hg had a faster decline in eGFR with age (0.91 ml/min per 1.73 m^2), whereas the decline in the 3 other groups was similar. Further stratification on the use of BP-lowering drugs revealed similar patterns in participants using and not using BP-lowering drugs, although the difference in eGFR decline between the participants with SBP ≥140 mm Hg and the other 3 groups was smaller in participants using BP-lowering drugs (Supplementary Figure S2 and Supplementary Table S2). The decline of eGFR with age was not different for the determinants studied when looking at

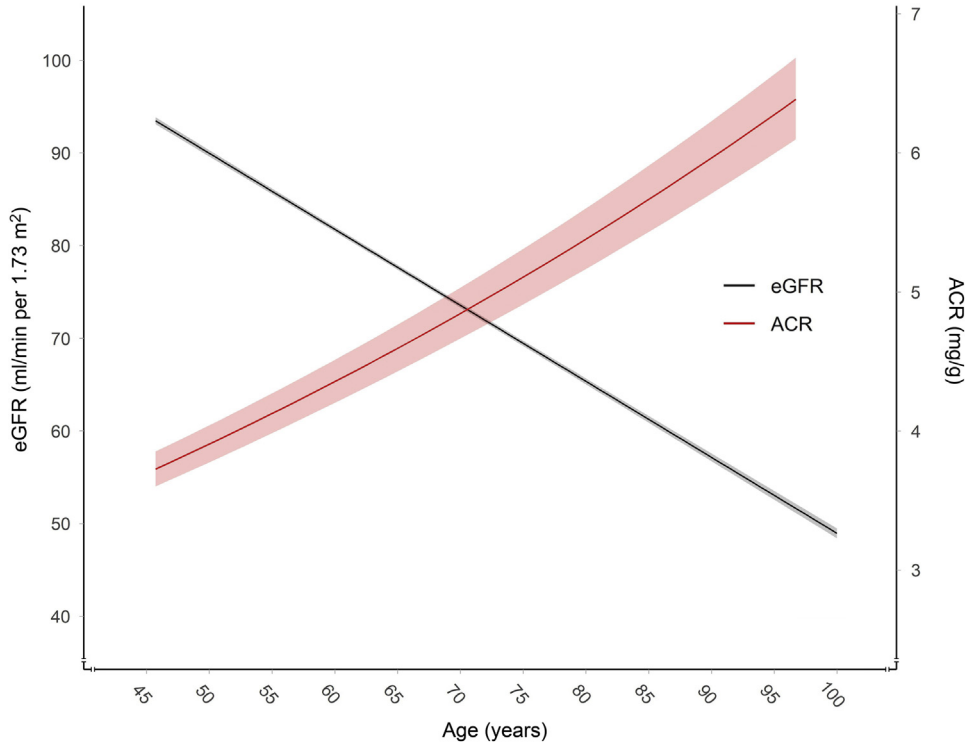

Figure 1. Longitudinal evolution of creatinine-based eGFR (ml/min per 1.73 m^2, $n = 12{,}062$) and urine albumin-creatinine ratio (mg/g, $n = 3522$) with age. ACR, albumin-to-creatinine ratio; eGFR, estimated glomerular filtration rate.

men and women separately (Supplementary Figure S3). The decline of eGFR with age in never smokers without hypertension, diabetes, and a history of CVD was 0.75 ml/min per 1.73 m^2 ($P < 0.001$, data not shown).

Age-Related Increase in Albuminuria

In total, 3522 participants had at least 1 measurement of the ACR, resulting in a total number of repeated measurements of 5995. A gradual increase in ACR was reported with age, with an annual increase of 0.05 mg/g ($P < 0.001$, Figure 1). The explained variability of ACR for the skeletal muscle index was 0.1% (data not shown). Stratification analyses revealed differences in the evolution of the ACR for all studied determinants (Figure 3). Men had a lower ACR at the age of 45 years compared with women. However, a faster increase with age was seen in men compared with women (increase in ACR of 0.11 vs. 0.01 mg/g per year increase in age, Supplementary Table S3), and the lines crossed around the age of 65 years. The rate of the ACR increase with age was similar in the 3 BMI groups. However, a higher ACR was reported at all ages in participants with a BMI $\geq$30 kg/m^2. Stratification on smoking status revealed the fastest increase in ACR with age in current smokers (increase of 0.10 mg/g per year increase in age). In addition, the increase in ACR with age in past smokers (annual increase of 0.06 mg/g) was higher compared with never smokers (annual increase of 0.03 mg/g). There was a difference in ACR increase when stratifying by SBP, with the fastest increase reported in participants with a SBP between 130 and 140 mm Hg (annual increase of 0.06 mg/g). Further stratification on the use of BP-lowering drugs revealed the fastest increase in ACR in participants with a SBP between 130 to 140 and $\geq$140 mm Hg when not using BP-lowering drugs, whereas no differences in the rates of increase were reported between the 4 groups determined by SBP when using BP-lowering drugs until the age of 80 years (Supplementary Figure S4 and Supplementary Table S2). After the age of 80 years, a faster increase in ACR was reported in participants with a SBP $<$120 mm Hg compared with those with a SBP $\geq$140 mm Hg. Participants with a history of CVD, hypertension, or prediabetes had a faster increase in ACR with age compared with the participants without these comorbidities. The ACR increase with age was similar in participants with and without diabetes, but ACR was higher at all ages in participants with diabetes. Results of the log-transformed ACR are found in Supplementary Figures S5 to S7.

DISCUSSION

In this study, we identified an average decline in eGFR of 0.82 ml/min per 1.73 m^2 and an increase in albuminuria of 0.05 mg/g with age. With regard to the evolution with age of both eGFR and ACR, male sex, hypertension,

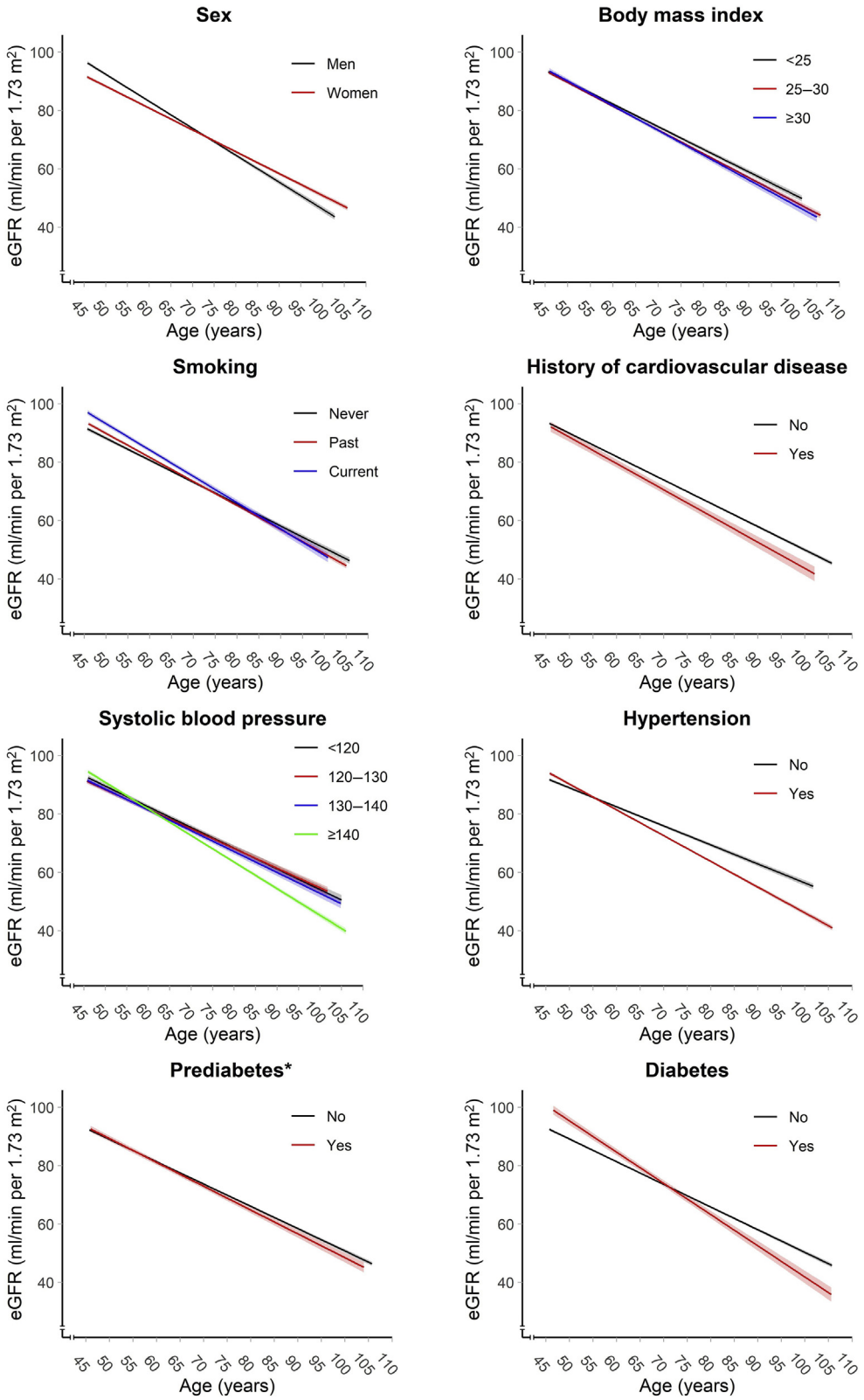

Figure 2. Longitudinal evolution of creatinine-based eGFR with age, stratified on sex, body mass index, smoking, history of cardiovascular disease, systolic blood pressure, hypertension, prediabetes, and diabetes (n = 12,062). *For the analysis of prediabetes, prevalent cases of diabetes were excluded (n = 10,818). eGFR, estimated glomerular filtration rate.

diabetes, smoking, and a history of CVD were identified as determinants. In addition, prediabetes was identified as determinant of ACR increase only. In people who never smoked and did not have diabetes, hypertension, or a history of CVD, the average annual eGFR decline was 0.75 ml/min per 1.73 m^2. Although the identified

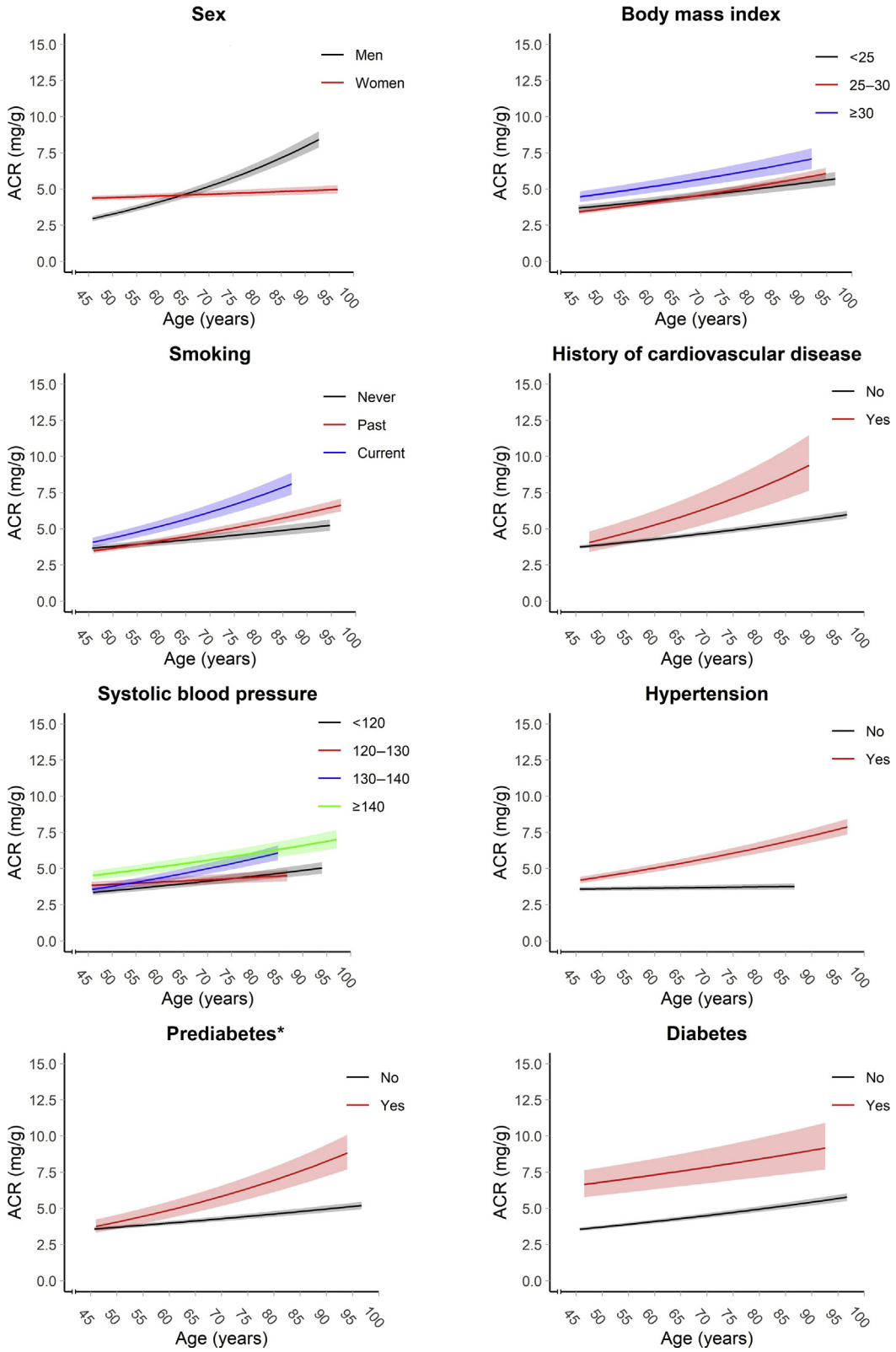

Figure 3. Longitudinal evolution of the urine albumin-creatinine ratio (mg/g) with age, stratified on sex, body mass index, smoking, history of cardiovascular disease, systolic blood pressure, hypertension, prediabetes, and diabetes ($n = 3522$). *For the analysis of prediabetes, prevalent cases of diabetes were excluded ($n = 3174$). ACR, albumin-to-creatinine ratio.

determinants are largely in line with previous literature, our study also identified several novel associations with potential implications for personalized medicine and public health.

First, our data add to the ongoing debate whether subjects with healthy aging may be labeled as having CKD. CKD has been defined using a fixed threshold of eGFR lower than 60 ml/min per 1.73 m^2 for at least 3

months.[34] Recently, however, the need for an age-adapted definition has been proposed.[35,36] One of the arguments to include such an age-adapted definition is that the current definition does not distinguish between eGFR decline due to kidney disease and eGFR decline due to healthy aging.[36] Our findings reveal the presence of healthy kidney function decline with age and therefore reiterate the consideration to include healthy aging of the kidney when defining CKD. Although at the individual level the differences in annual decline rates are modest, from a public health point of view, these differences would reclassify a substantial proportion of the general population and could prevent overdiagnosis.

Second, our data provide insight in whether the change in eGFR with age also occurs with ACR. Although a higher ACR with older age and a correlation between albuminuria and age have been reported in previous cross-sectional population-based studies,[37,38] the rate of increase over time has not been investigated previously. In fact, it has been suggested that urinary albumin excretion is stable and does not increase with healthy aging and that a potential increase in ACR is due to a decrease in muscle mass and not to a decrease in kidney function.[9,39] A recent longitudinal study indeed found that subjects with low skeletal muscle mass had an increased risk of albuminuria.[40] The explanation for this association is not fully clear. Lower urinary creatinine excretion with age may increase ACR, but insulin resistance and endothelial dysfunction were also suggested as possible explanations.[40] In the current study, we reveal that the skeletal muscle index explained only 0.1% of the variability in ACR. This implies that other factors must explain the increase of albuminuria with age in our population, such as hypertension, as we observed virtually no increase in albuminuria in participants without hypertension.

Third, our data add to the evolving concept of sex differences in CKD. This is often termed the "CKD paradox" to describe the observation of a higher prevalence of CKD in women, whereas men with CKD progress more rapidly to kidney failure.[41,42] However, in a previous cross-sectional study, a lower mean GFR with older age was reported for women compared with men.[43] In our study, we observed a higher annual eGFR decline in men compared with women, whereas men had higher eGFR levels at younger age, which is in line with the "CKD paradox." Similarly, we report a higher annual increase in albuminuria in men compared with women, whereas men had lower starting levels. These sex differences could be explained by the direct effects of sex hormones on the kidney or sex differences in lifestyle factors not captured by variables such as BMI or smoking.[42,44] Of note, we found no differences in eGFR for all studied determinants when looking at men and women separately.

Fourth, participants with prediabetes had a higher annual increase in albuminuria than participants without prediabetes. Because no differences in the eGFR decline with age were found when stratifying by prediabetes, our data suggest that prediabetes causes selective damage to the glomerular filtration barrier which is not yet affecting kidney function. This may provide a window of opportunity to prevent deterioration of kidney function when prediabetes evolves to diabetes. However, prediabetes is currently not considered in the cardiovascular risk management or prevention strategies. Our results for participants with diabetes agree with previous findings,[26] including a higher annual eGFR decline and higher ACR compared with participants without diabetes. The higher baseline eGFR in participants with diabetes is compatible with initial hyperfiltration.[45]

Finally, another novel association was a higher baseline eGFR and higher rate of eGFR decline in current smokers compared with past and never smokers. Previously, only cross-sectional studies have been conducted, reporting higher eGFR levels in current smokers compared with past and never smokers and an increased risk of proteinuria with smoking.[46–49] In addition, similar to our study, the associations between smoking and eGFR were most pronounced in current smokers compared with past smokers, suggesting the effect of smoking is, at least partly, reversible after discontinuation of smoking.[48] The mechanism underlying our and previous findings is incompletely understood, but glomerular hyperfiltration is suggested to play a role.[46] Smoking could induce repeated transient decreases in renal plasma flow and GFR,[50,51] resulting in glomerular damage.[46] This could result in compensatory hypertrophy and hyperfiltration of the remaining glomeruli,[48,52] eventually contributing to CKD.[52]

Strengths of our study include the large number of participants with longitudinal assessments of kidney function in a population-based cohort study with a long follow-up period. Furthermore, by using a novel modeling technique, we were able to limit the chance of selection bias introduced by the possible presence of nonrandom dropout. A limitation of our study is the small number of repeated measurements of albuminuria and the unavailability of repeated measurements of serum cystatin C as an alternative marker of kidney function. This is especially important because of the potential underestimation of eGFR (decline) estimated by serum creatinine in participants with hyperfiltration, such as in patients with diabetes.[53] In addition, our study only includes Caucasian participants

aged 45 years or older, limiting the generalizability of our results to other populations. Furthermore, selection bias cannot be fully eliminated as we included general practitioner data, although we found the Rotterdam Study and general practitioner data to be comparable. Finally, previous literature has suggested that the age-related decline in eGFR starts between the ages of 30 and 40 years,[2,7,54,55] which we could not investigate in our study, as our study population is aged 45 years and older.

In conclusion, we report a decline in eGFR and an increase in albuminuria with age in the middle-aged and elderly of the general population, dependent on several individual characteristics. These characteristics are currently not taken into account when defining healthy kidney aging. Our findings highlight the importance of considering the implementation of the rate of kidney function decline with healthy aging in the definition of CKD to prevent potential over-diagnosis of CKD in elderly. Several potential determinants of kidney function decline were identified in the current study and this knowledge can be used to improve prediction, personalized medicine, and public health, for example in people with prediabetes or smokers.

DISCLOSURE

All the authors declared no competing interests.

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary methods

Table S1. Overall and sex-specific eGFR decline per year increase in age, separately for sex, body mass index, smoking, history of cardiovascular disease, systolic blood pressure, hypertension, prediabetes, and diabetes.

Table S2. Decline in eGFR and increase in urine ACR per year increase in age, stratified on systolic blood pressure and the use of blood pressure-lowering drugs.

Table S3. Overall and sex-specific increase in urine ACR per year increase in age, separately for sex, body mass index, smoking, history of cardiovascular disease, systolic blood pressure, hypertension, prediabetes, and diabetes.

Figure S1. Flowchart of the study population.

Figure S2. Longitudinal evolution of creatinine-based eGFR with age, stratified on systolic blood pressure and the use of blood pressure-lowering drugs.

Figure S3. Longitudinal evolution of creatinine-based eGFR with age stratified on sex, body mass index, smoking, history of cardiovascular disease, systolic blood pressure, hypertension, prediabetes, and diabetes.

Figure S4. Longitudinal evolution of the urine albumin-creatinine ratio with age (mg/g), stratified on systolic blood pressure and the use of blood pressure-lowering drugs.

Figure S5. Longitudinal evolution of the log urine albumin-creatinine ratio (logACR, mg/g) with age (n = 3522).

Figure S6. Longitudinal evolution of the log urine albumin-creatinine ratio (logACR, mg/g) with age, stratified on sex, body mass index, smoking, history of cardiovascular disease, systolic blood pressure, hypertension, prediabetes, and diabetes.

Figure S7. Longitudinal evolution of the log urine albumin-creatinine ratio with age (logACR, mg/g), stratified on systolic blood pressure and the use of blood pressure-lowering drugs.

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