



## Original article

## Association of habitual coffee consumption and kidney function: A prospective analysis in the Rotterdam Study



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## SUMMARY

**Background & aims:** Population-based studies have suggested a protective effect of coffee against development of chronic kidney disease (CKD), possibly through coffee's anti-inflammatory and antioxidant compounds. Studies on coffee and kidney function decline in the general population are scarce. We studied associations of habitual coffee consumption with repeated assessments of estimated glomerular filtration rate (eGFR) and urinary albumin-to-creatinine ratio (ACR).

**Methods:** We used data from 7,914 participants of the population-based Rotterdam Study. Baseline coffee consumption data (cups/day) were obtained from home interviews and validated food frequency questionnaires (1997–2008). Repeated assessments of eGFR (ml/min per 1.73 m<sup>2</sup>, 1997–2014) were calculated according to the creatinine-based CKD Epidemiology Collaboration equation of 2012. Repeated assessments of urinary albumin and creatinine were used to estimate ACR (mg/g, 2006–2014). Data were analyzed by applying linear mixed models, adjusted for sociodemographic, lifestyle and dietary factors, and cardiovascular disease risk factors. Predefined subgroup analyses were performed stratified by CKD risk factors.

**Results:** Participants' mean (SD) baseline age was 66 (10) years, 57% were women and median [IQR] coffee consumption was 3.0 [2.0, 5.0] cups/day. Those drinking more coffee were more likely to smoke, and to have type 2 diabetes (T2D) and obesity. Mean eGFR was 79 (15) ml/min per 1.73 m<sup>2</sup>. In the total study population, coffee was not associated with longitudinal eGFR during a median of 5.4 years of follow-up ( $\beta = 0.04$  ml/min per 1.73 m<sup>2</sup> per one cup/day [95% CI: −0.10, 0.18]). However, among those aged >70 years, one additional coffee cup/day was associated with on average 0.84 (0.51, 1.18) ml/min per 1.73 m<sup>2</sup> higher longitudinal eGFR. Among obese participants this estimate was 0.32 (0.01, 0.63). A protective trend was also observed among former smokers (0.17 [−0.03, 0.39]) and those with T2D (0.42 [−0.05, 0.88]). Coffee was not associated with longitudinal ACR (0.01 mg/ml [−0.01, 0.02]).

**Conclusion:** While coffee was not associated with eGFR and ACR in the total population, more coffee consumption was associated with higher longitudinal eGFR among those at higher risk for CKD, i.e., among those aged 70+ and obese participants. These findings require confirmation in other prospective cohort studies.

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## 1. Introduction

Chronic kidney disease (CKD) is a long-term condition characterized by progressive kidney function decline with an estimated global prevalence of 13% [1]. Despite medical prevention strategies,

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kidney function decline, usually estimated by glomerular filtration rate (eGFR), is accelerated in those with type 2 diabetes (T2D) and other cardiovascular risk factors [2–4]. This calls for targeted strategies to delay kidney function decline in ageing and high-risk populations.

We previously showed that a healthy diet (e.g. Dietary Approaches to Stop Hypertension or Mediterranean diet) could represent such a strategy, as it was consistently associated with lower risk of CKD in the general population [5]. Also specific dietary components have been linked to kidney function, of which coffee has been suggested to be promising for reducing risk of CKD [5]. Coffee contains more than 1000 bioactive compounds [6], including for example caffeine, chlorogenic acids, cafestol and kahweol. Some of these bioactives have anti-inflammatory and antioxidant properties. This could explain previously observed beneficial associations of coffee, both caffeinated and decaffeinated, with T2D [7,8] and hypertension [9]. T2D and hypertension are major risk factors of CKD [10], and reduced kidney function and kidney damage are well-known diabetic complications. Therefore, it is important to further study whether coffee may also have beneficial effects on markers of kidney function (eGFR) or kidney damage (urinary albumin-to-creatinine ratio, ACR).

Higher coffee consumption has been linked to improved kidney function, although evidence remains inconclusive. Observational studies, including one Mendelian Randomization (MR) study, have reported either an association of higher coffee consumption with decreased risk of CKD [11,12], albuminuria [13], or kidney failure [14] or no association with CKD [15]. However, so far only one study ( $n = 3,798$ ; 15 years follow-up) has been performed on the association of coffee with repeated assessments of eGFR [16]. This population-based study found that coffee was associated with a slightly higher eGFR, but only in those aged  $\geq 46$  years. Associations of coffee with repeated assessments of eGFR have not yet been performed among other high CKD-risk groups (e.g. those with hypertension or T2D). Assessing the associations in these subgroups may be important, as they may benefit more from coffee given their high inflammation levels [17]. Furthermore, studies linking coffee with repeated measurements of urinary ACR are lacking.

Therefore, we investigated associations between habitual coffee consumption and repeated assessments of eGFR and urinary ACR in a population-based cohort. We further assessed whether associations with eGFR varied by predefined subgroups according to CDK risk factors.

## 2. Materials and methods

### 2.1. Study design and study population

We used data of the Rotterdam Study (RS), an ongoing population-based cohort study in the district Ommoord, Rotterdam, the Netherlands. Its design has been described in detail elsewhere [18]. Briefly, the first sub-cohort started in 1989–93 and 7,983 participants aged  $\geq 55$  years were enrolled (RS-I). During 2000–01, another 3,011 participants who had become 55 years of age since the start of the study or who migrated into the study district were enrolled in the second sub-cohort (RS-II). The third sub-cohort (RS-III) was established in 2006–08, for which 3,932 participants aged  $\geq 45$  y were recruited. In total, 14,926 participants were enrolled at baseline. Follow-up examinations were performed every 4–6 years for each sub-cohort.

The current study used data of the third follow-up examination of the first cohort (RS-I-3), and the first examinations of the second and third cohort (RS-II-1 and III-1) as baseline. Follow-up

data were collected during the succeeding visits (RS-I-4, I-5; RS-II-2, II-3; and RS-III-2). We excluded 308 participants who did not give consent for follow-up, and 1,415 RS-I participants who died before the start of RS-I-3, baseline of the current study. Of the remaining sample, 8,718 participants filled out questionnaires about dietary intake, from which we excluded 47 participants with implausible energy intake ( $<500$  or  $>5000$  kcal/day). This resulted in 8,671 participants with available coffee intake data. Of this group, 7,914 participants had at least one eGFR assessment for analyses of longitudinal eGFR. For the analysis of incident reduced kidney function, we selected participants with eGFR assessments at baseline and at least one follow-up visit, followed by exclusion of participants with baseline eGFR  $<60$  ml/min per  $1.73$  m<sup>2</sup>. The final analytical sample size for this analysis was 4,649. Repeated measurements of urinary ACR were available for participants of RS-III only and were performed in the same study population as analyses for eGFR. After applying the same exclusion criteria used in the main coffee-eGFR analyses, the final analytical sample size for the study of longitudinal urinary ACR was 2,505 (Fig. 1). The Rotterdam Study has been approved by the medical ethics committee of Erasmus MC and by the Dutch Ministry of health, Welfare and Sport. All participants provided written informed consent.

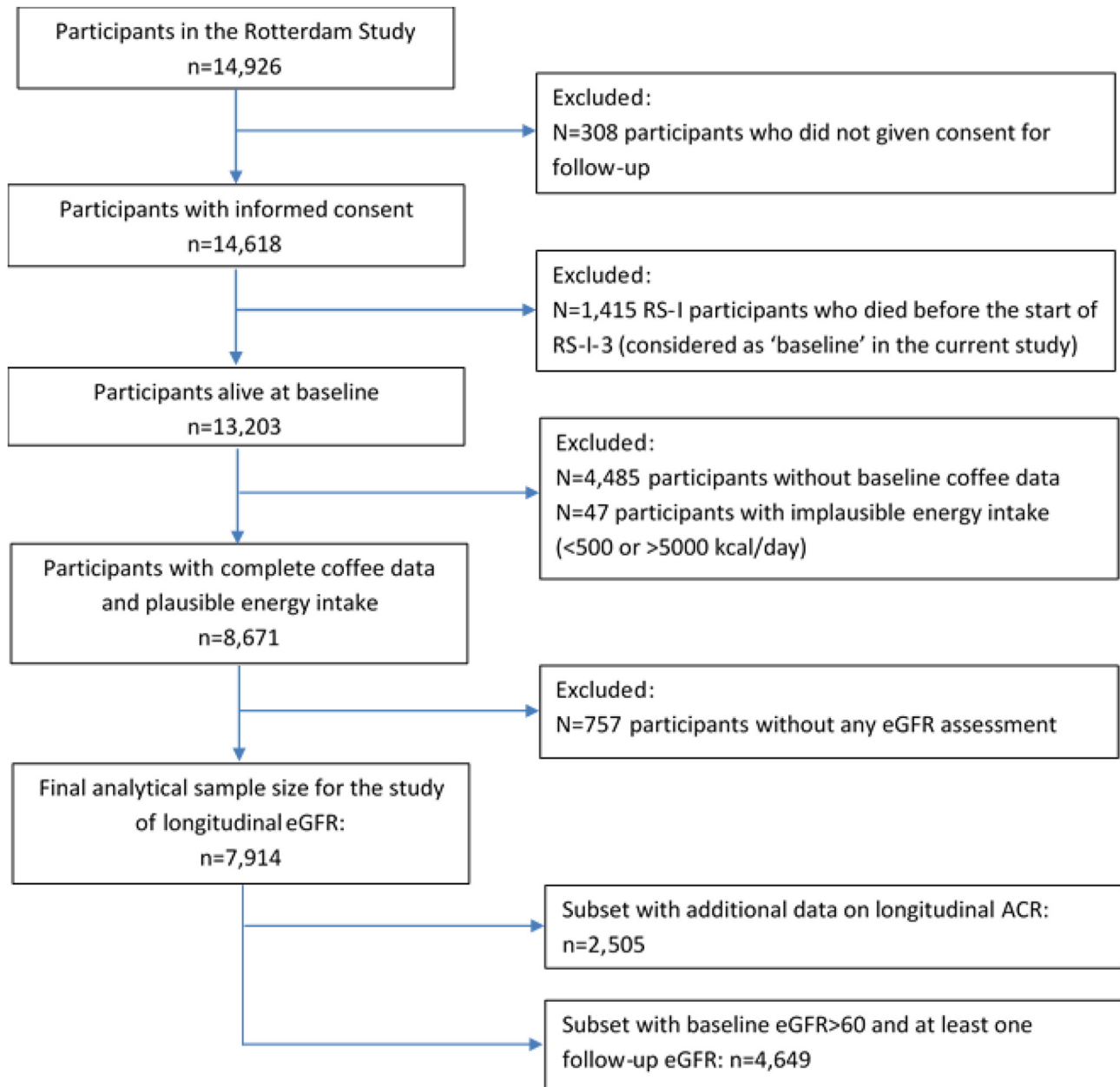
### 2.2. Coffee consumption

Baseline data on habitual total coffee consumption were obtained through home interviews (RS-I-3) and validated 170-item (RS-II-1) and 389-item (RS-III-1) food frequency questionnaires (FFQs). During the home interviews, participants were asked if they consumed coffee and its frequency was reported in cups/day. In both FFQs, participants were asked about the frequency and amount of foods and beverages habitually consumed in the past, including the frequency of coffee consumption (170-item FFQ: reported in 'cups/day'; 389-item FFQ: reported in 'number of days per month or per week' and 'cups/day'). A standard Dutch coffee cup's serving size is 125 mL.

### 2.3. Kidney function

Serum creatinine was determined at baseline (RS-I-3, RS-II-1, RS-III-1) and follow-up visits (RS-I-4, I-5; RS-II-2, II-3; RS-III-2) using an enzymatic assay method, performed by the Erasmus MC AKC laboratory in all three cohorts. Creatinine levels were calibrated by aligning its mean values with those of the Third National Health and Nutrition Examination Survey (NHANES III) in different sex and age specific categories ( $<50$ , 50–59, 60–69,  $\geq 70$ ) [19]. Urinary ACR measurements were also performed at Erasmus MC AKC laboratory by using a Roche Modular P800. For albumin, the lower detection limit was 3 mg/L, and this was 61 mg/L for creatinine. Urinary ACR was estimated by dividing urine albumin by urine creatinine (mg/g).

eGFR was calculated according to the CKD Epidemiology Collaboration (CKD-EPI) equation of 2012, based on age, sex, race and serum creatinine alone [19]. The primary outcome was changes in longitudinal eGFR, for which negative betas indicated a deterioration and positive betas indicated an improvement of kidney function during follow-up. One of the secondary outcomes was incident reduced kidney function, defined as a single assessment of eGFR  $<60$  ml/min per  $1.73$  m<sup>2</sup> at follow-up, and was used as proxy for incident CKD. Another secondary outcome was changes in longitudinal ACR, with negative betas indicating less kidney damage and positive betas indicating more kidney damage during follow-up.



**Fig. 1.** Flowchart describing the population for analysis. Abbreviations: kcal, kilocalorie; eGFR, estimated glomerular filtration rate; ACR, albumin-to-creatinine ratio.

#### 2.4. Covariate assessment

Data on the highest attained level of education, smoking and physical activity were obtained through self-reported questionnaires. Education attainment was defined as primary (primary education), low (lower/intermediate general education or lower vocational education), intermediate (intermediate vocational education or higher general education) or high (higher vocational education or university), according to United Nations Educational, Scientific and Cultural Organization (UNESCO) classification [20]. Smoking status was categorized as never, former or current. Information about physical activity was obtained through the validated Zutphen [21] (RS-I and RS-II) and LASA [22] (RS-III) questionnaires and expressed in metabolic equivalent of task (MET) hours/week. A diet quality score reflecting adherence to the Dutch dietary guidelines (scores ranging from 0 [no adherence] to 14 [full

adherence]) was calculated from data obtained with the FFQs, as explained elsewhere [23]. Macronutrient (g/day) and micronutrient (mg/day) intakes were calculated using Dutch food composition tables. Baseline data on alcohol (glasses/day) and tea consumption (cups/day, one cup equals 125 mL) were obtained through home interviews (RS-I-3) and validated 170-item (RS-II-1) and 389-item (RS-III-1) FFQs. Baseline physical measures and collection of blood samples were assessed at the research center. Body mass index (BMI, in kg/m<sup>2</sup>) was calculated as weight (kg) divided by height (meters) squared. Blood lipids (mmol/L) were analyzed in fasting blood samples, using the cholesterol-oxidase-peroxidase (CHO-POD) enzymatic reaction for total cholesterol (with an AU5800 chemistry analyser), and an enzyme immune-inhibition method for HDL-cholesterol (with Beckman Coulter). Hypercholesterolemia is defined as total serum cholesterol  $\geq 6.5$  mmol/L and/or lipid reducing drug use. Blood pressure

(mmHg) was measured at the right brachial artery with the participant in sitting position. The mean of two consecutive measurements was used. Hypertension was defined as high blood pressure (systolic blood pressure [SBP]  $\geq 140$  mmHg or diastolic blood pressure [DBP]  $\geq 90$  mmHg) or use of blood pressure lowering drugs. Cardiovascular disease (CVD) was defined as having coronary heart disease and/or stroke. T2D was considered present in case of a self-reported physician's diagnosis, use of glucose lowering drugs or elevated glucose levels ( $\geq 7.0$  mmol/L if fasted or  $\geq 11.1$  mmol/L if not fasted). Blood glucose (mmol/L) was measured using the hexokinase method [24]. Medication data were obtained from both pharmacy records and home interviews and were coded according to the Anatomical Therapeutic Chemical (ATC) Classification System [18].

## 2.5. Statistical analysis

Histograms and QQ-plots were used to check for normality of the data. Normally distributed variables were described using mean (standard deviation [SD]). The median (interquartile range [IQR]) and frequency (%) were used for skewed numerical and categorical variables, respectively.

Coffee consumption was analyzed continuously (per one cup/day increase). A dose-response relationship between coffee as categorical variable and eGFR was also investigated. Based on the distribution of the data, we categorized coffee consumption as follows: none,  $>0$ –2 cups/day (low),  $>2$ –4 cups/day (moderate),  $>4$  cups/day (heavy). Due to the small number of non-consumers ( $n = 279$ ), which would have made it an unstable reference group in the models, the  $>0$ –2 group was chosen as the reference group in the categorical analyses. The  $P_{\text{trend}}$  was determined by treating the categorical variable as a continuous variable in the models. Data for urinary ACR were natural log-transformed to obtain normally distributed data. Linear mixed models with both random intercept (participants) and slope (time) were used to study repeated assessments of eGFR and natural log-transformed urinary ACR. Results are presented as beta coefficients with corresponding 95% confidence interval (CI). Associations between habitual coffee consumption and incident reduced kidney function were examined using Cox proportional hazards regression, for which results are reported as hazard ratio (HR) with its 95% CI. Follow-up time in years from baseline until the event (date of blood sampling used as proxy), death, or withdrawal from the study, was used as timescale. The proportional hazards assumption was checked by visual inspection of Schoenfeld residuals plots and was met.

Three statistical models were created. The potential confounders were selected *a priori*, based on previous literature and biological knowledge. Model one was adjusted for age (years), sex (2 categories), highest level of attained education (4 categories) and sub-cohort (3 categories). Model two was additionally adjusted for lifestyle and dietary factors, including smoking status (3 categories), physical activity (MET hours/week), diet quality (score), alcohol consumption (glasses/day), tea consumption (cups/day), and energy intake (kcal/day). Finally, model three took into account classic cardiovascular risk factors (SBP [mmHg], total serum cholesterol [mmol/L], and BMI [ $\text{kg}/\text{m}^2$ ]) and blood pressure lowering drug use (2 categories), because these variables could be confounders, but also mediators [25].

### 2.5.1. Additional analyses

To investigate to what extent CKD risk factors modified coffee's association with longitudinal eGFR, predefined subgroup analyses stratified by age ( $\leq 60$ ,  $>60$ –70,  $>70$  y), sex, smoking status (never, former, current), BMI category ( $\leq 25$ ,  $>25$ –30,  $>30$   $\text{kg}/\text{m}^2$ ) and presence of hypertension, T2D, CVD or hypercholesterolemia were

conducted. Effect modification was also evaluated by including interaction terms between coffee consumption and the stratifying variable in model 3.

Three sets of sensitivity analyses were performed. Firstly, non-consumers were excluded from the main and stratified analyses, to check if results were driven by non-coffee drinkers. In a second and third sensitivity analysis, outliers in coffee consumption (median  $+3 \times \text{IQR}$ ) and eGFR (mean  $+4 \times \text{SD}$ ) were excluded from the main analysis.

Missing data (0.1–14%) for covariates were addressed by performing multiple imputation by chained equations, with 10 imputations and 10 iterations, by using the MICE package for R software [26]. The analyses were performed in each imputed dataset separately, and the estimates were subsequently pooled using Rubin's rules [27]. RStudio 4.0.3 was used for all analyses and a two-side  $p$ -value  $<0.05$  was considered statistically significant.

## 3. Results

### 3.1. Baseline characteristics

At baseline, participants had a mean age of 66 (10) years, and 57% were women. The mean eGFR was 79 (15) ml/min per  $1.73 \text{ m}^2$ . More than 50% of the individuals had hypertension, and 10% had T2D or CVD. BMI was 27 (4)  $\text{kg}/\text{m}^2$ , and 21% of the study population had obesity. The median [IQR] total coffee intake was 3.0 [2.0, 5.0] cups/day; 4% of the participants were non-coffee drinkers. Compared to non-coffee consumers, heavy coffee consumers ( $>4$  cups/day) were more often men, more likely to smoke, to drink higher amounts of alcohol, and they had the highest energy intake (Table 1, Supplemental Table 1).

The baseline characteristics of participants with and without available coffee data are presented in Supplemental Table 2.

### 3.2. Coffee consumption and kidney function

The mean eGFR declined on average with 4.92 ml/min per  $1.73 \text{ m}^2$  over a median of 5.4 years of follow-up. The total number of repeated eGFR assessments was 13,798 (median of 2 assessments per participant). In the total study population and after adjustment for confounders (model 3), coffee was not associated with longitudinally assessed eGFR during follow-up in either continuous analyses ( $\beta = 0.04$  ml/min/ $1.73 \text{ m}^2$  per one cup/day [95% CI  $-0.10, 0.18$ ]), or for coffee in categories (Table 2). Excluding outliers in both exposure and outcome yielded similar results (Supplemental Table 3).

Coffee-eGFR associations were consistent for both sexes ( $P_{\text{interaction}} = 0.45$ ), but not for different age groups (Fig. 2a,  $P_{\text{interaction}} < 0.001$ ). Among those aged  $>70$  years, consuming one additional cup of coffee per day was associated with 0.84 ml/min per  $1.73 \text{ m}^2$  higher eGFR during follow-up (model 3: 0.84 [95% CI 0.51, 1.18]; Fig. 2a). This association became stronger after exclusion of non-coffee drinkers (Supplemental Table 4). No significant findings were observed in the younger age groups (Fig. 2a, Supplemental Table 4). Age and sex stratified associations for coffee in categories yielded similar results (Table 3). Smoking status did not modify the coffee-eGFR association ( $P_{\text{interaction}} > 0.05$ ; Fig. 2a), although among former smokers, we observed a non-significant trend of higher coffee consumption with higher eGFR (0.17 [95% CI  $-0.03, 0.39$ ] per one cup/day increase). No associations with eGFR were found in never and current smokers, in either continuous or categorical analyses (Fig. 2a, Table 3, Supplemental Table 4).

Hypertension, CVD, or hypercholesterolemia did not modify the coffee-eGFR association (Fig. 2b,  $P_{\text{interaction}} > 0.05$ ). Among T2D subjects, we observed a trend for coffee with higher eGFR during

**Table 1**

Baseline characteristics of 7,914 participants of the Rotterdam Study, overall, and stratified by coffee consumption categories.

|                                         | Total cohort       | Coffee consumption (cups/day) |                   |                        |                   |
|-----------------------------------------|--------------------|-------------------------------|-------------------|------------------------|-------------------|
|                                         |                    | 0 (non-consumers)             | >0-2 (low intake) | >2-4 (moderate intake) | >4 (heavy intake) |
| N                                       | 7,914              | 279                           | 2,026             | 3,423                  | 2,186             |
| Coffee consumption, cups/day            | 3.25 [2.00, 5.00]  | 0.00 [0.00, 0.00]             | 2.00 [1.00, 2.00] | 3.25 [3.00, 4.00]      | 6.00 [5.11, 6.96] |
| <b>Sociodemographic factors</b>         |                    |                               |                   |                        |                   |
| Age, y                                  | 65.5 (9.6)         | 60.2 (9.3)                    | 68.2 (10.3)       | 66.2 (9.3)             | 62.6 (8.2)        |
| Sex, n(%)                               |                    |                               |                   |                        |                   |
| Men                                     | 3,415 (43.2)       | 97 (34.8)                     | 740 (36.5)        | 1,408 (41.1)           | 1,170 (53.5)      |
| Women                                   | 4,499 (56.8)       | 182 (65.2)                    | 1,286 (63.5)      | 2,015 (58.9)           | 1,016 (46.5)      |
| Education, n(%)                         |                    |                               |                   |                        |                   |
| Primary                                 | 972 (12.3)         | 29 (10.4)                     | 299 (14.8)        | 411 (12.0)             | 233 (10.7)        |
| Intermediate                            | 3,181 (40.2)       | 96 (34.4)                     | 827 (40.8)        | 1,424 (41.6)           | 834 (38.2)        |
| Higher general                          | 2,295 (29.0)       | 86 (30.8)                     | 564 (27.8)        | 993 (29.0)             | 652 (29.8)        |
| University                              | 1,399 (17.7)       | 66 (23.7)                     | 323 (15.9)        | 558 (16.3)             | 452 (20.7)        |
| <b>Lifestyle factors</b>                |                    |                               |                   |                        |                   |
| Smoking status, n(%)                    |                    |                               |                   |                        |                   |
| Never                                   | 2,474 (31.3)       | 133 (47.7)                    | 787 (38.8)        | 1,084 (31.7)           | 470 (21.5)        |
| Former                                  | 3,771 (47.6)       | 98 (35.1)                     | 980 (48.4)        | 1,725 (50.4)           | 968 (44.3)        |
| Current                                 | 1,655 (20.9)       | 48 (17.2)                     | 258 (12.7)        | 606 (17.7)             | 743 (34.0)        |
| Physical activity, METh/wk              | 70.1 [40.3, 103.4] | 60.2 [29.0, 93.6]             | 69.1 [41.0, 104]  | 71.6 [44.2, 104]       | 69.3 [34.8, 104]  |
| <b>Cardiovascular risk factors</b>      |                    |                               |                   |                        |                   |
| BMI, kg/m <sup>2</sup>                  | 27.2 (4.2)         | 26.7 (4.8)                    | 27.0 (4.1)        | 27.2 (4.1)             | 27.4 (4.3)        |
| Overweight, n(%)                        | 3,657 (46.2)       | 121 (43.4)                    | 921 (45.5)        | 1,624 (47.4)           | 991 (45.3)        |
| Obesity, n(%)                           | 1,634 (20.6)       | 49 (17.6)                     | 397 (19.6)        | 701 (20.5)             | 487 (22.3)        |
| Serum lipids, mmol/L                    |                    |                               |                   |                        |                   |
| Total cholesterol                       | 5.74 (1.02)        | 5.60 (1.09)                   | 5.73 (1.05)       | 5.77 (1.00)            | 5.71 (1.00)       |
| HDL                                     | 1.41 (0.41)        | 1.43 (0.40)                   | 1.42 (0.44)       | 1.42 (0.39)            | 1.37 (0.39)       |
| Hypercholesterolemia, n(%)              | 2,833 (35.8)       | 105 (37.6)                    | 753 (37.2)        | 1,198 (35.0)           | 777 (35.5)        |
| Fasting glucose, mmol/L                 | 5.50 [5.10, 6.00]  | 5.40 [5.00, 5.70]             | 5.50 [5.10, 6.10] | 5.50 [5.10, 6.00]      | 5.50 [5.10, 6.00] |
| T2D, n(%)                               | 917 (11.6)         | 25 (9.0)                      | 267 (13.2)        | 382 (11.2)             | 243 (11.1)        |
| SBP, mmHg                               | 139.8 (21.2)       | 135.3 (21.0)                  | 141.2 (22.2)      | 140.3 (21.1)           | 138.2 (20.1)      |
| Hypertension, n(%)                      | 4,926 (62.2)       | 150 (53.8)                    | 1,380 (68.1)      | 2,154 (62.9)           | 1,242 (56.8)      |
| CVD, n(%)                               | 709 (9.0)          | 18 (6.5)                      | 220 (10.9)        | 299 (8.7)              | 172 (7.9)         |
| <b>Medication use, n(%)<sup>a</sup></b> |                    |                               |                   |                        |                   |
| Antihypertensive drugs                  | 2,530 (32.0)       | 86 (30.8)                     | 772 (38.1)        | 1,100 (32.1)           | 572 (26.2)        |
| <b>Kidney function</b>                  |                    |                               |                   |                        |                   |
| eGFR, ml/min/1.73 m <sup>2</sup>        | 78.8 (14.9)        | 83.6 (14.6)                   | 76.2 (16.3)       | 78.1 (14.4)            | 81.8 (13.8)       |
| eGFR <60, n(%)                          | 837 (10.6)         | 16 (5.7)                      | 314 (15.5)        | 363 (10.6)             | 144 (6.6)         |

Normally distributed variables are described in means (standard deviation), skewed variables in median [interquartile range], and categorical variables in numbers (%). Overweight is defined as BMI >25–30 kg/m<sup>2</sup>. Obesity is defined as BMI >30 kg/m<sup>2</sup>. Hypercholesterolemia is defined as total serum cholesterol ≥6.5 mmol/L and/or lipid reducing drug use. T2D is present in case of self-reported physician's diagnosis, use of glucose lowering drugs, or elevated plasma glucose level (≥7 mmol/L if fasted for ≥4 h or ≥11.1 mmol/L if not fasted). Hypertension is present in case of SBP ≥140 mmHg or diastolic blood pressure ≥90 mmHg and/or blood pressure lowering drug use. CVD is defined as coronary heart disease and/or stroke. Abbreviations: N, sample size; MET, metabolic equivalent of task; BMI, body mass index; T2D, type 2 diabetes; SBP, systolic blood pressure; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate.

<sup>a</sup> Coded according to the ATC classification system: antihypertensive drugs (C02, C03, C07, C09).

follow-up (0.42 [95% CI -0.05,0.88]), but the interaction term was not significant ( $P_{\text{interaction}} > 0.05$ , Fig. 2b). BMI-stratified results showed that among those with BMI >30 kg/m<sup>2</sup>, one extra cup of coffee per day was associated with 0.32 ml/min per 1.73 m<sup>2</sup> (95%

CI 0.01,0.63) higher eGFR during follow-up (Fig. 2b). Exclusion of non-coffee drinkers resulted in even stronger associations (Supplemental Table 4). Analyses for coffee in categories suggested similar trends (Table 4).

**Table 2**

Multivariable adjusted associations between coffee consumption and longitudinal eGFR in 7,914 participants of the Rotterdam Study.

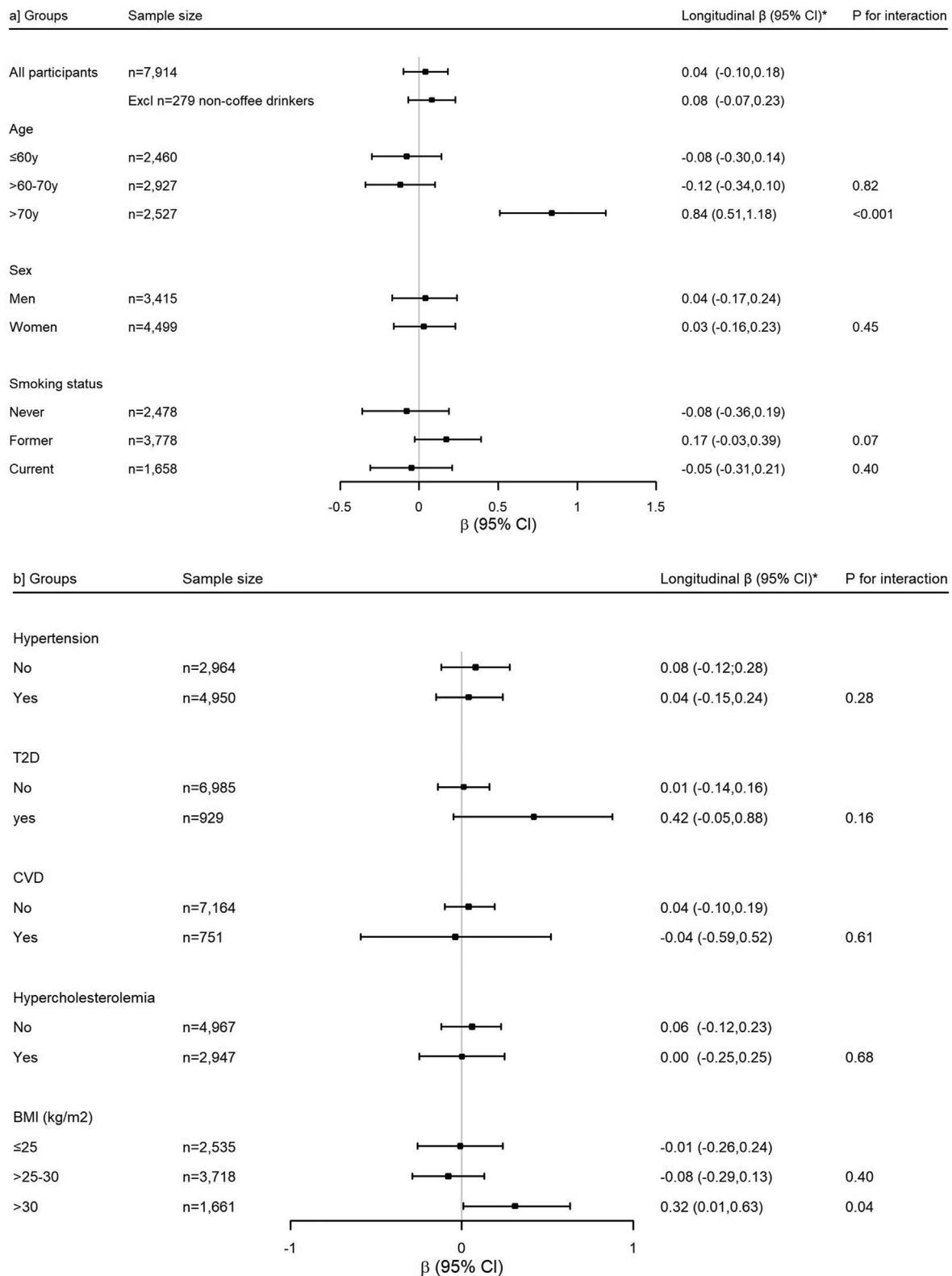
|         | Total coffee consumption (cups/day) |         |                   |                |                    |                   | P <sub>trend</sub> |
|---------|-------------------------------------|---------|-------------------|----------------|--------------------|-------------------|--------------------|
|         | Continuous                          |         | 0 (n=279)         | >0-2 (n=2,026) | >2-4 (n=3,423)     | >4 (n=2,186)      |                    |
|         | β (95% CI)                          | P-value | β (95% CI)        | β              | β (95% CI)         | β (95% CI)        |                    |
| Model 1 | 0.16 (0.02,0.30)                    | 0.02    | 0.81 (−0.73,2.36) | Ref            | 0.16 (−0.52,0.85)  | 0.92 (−0.14,1.69) | 0.05               |
| Model 2 | 0.07 (−0.08,0.21)                   | 0.37    | 0.95 (−0.60,2.50) | Ref            | 0.04 (−0.65,0.72)  | 0.44 (−0.36,1.23) | 0.43               |
| Model 3 | 0.04 (−0.10,0.18)                   | 0.55    | 0.93 (−0.61,2.47) | Ref            | −0.04 (−0.72,0.65) | 0.29 (−0.50,1.08) | 0.67               |

Values are regression coefficients (β) and corresponding 95% confidence intervals (95% CI) from linear mixed models of the association between coffee consumption per cup/day increase and in categories and longitudinal assessments of eGFR in ml/min per 1.73 m<sup>2</sup> during follow-up. Abbreviations: eGFR, estimated glomerular filtration rate; CI, confidence interval.

Model 1: adjusted for age (years), sex (2 categories), education (4 categories), and sub-cohort (3 categories).

Model 2: model 1 and additionally adjusted for smoking status (3 categories), physical activity (MET hours/week), diet quality (score), energy intake (kcal/day), alcohol consumption (glasses/day), and tea consumption (cups/day).

Model 3: model 2 and additionally adjusted for systolic blood pressure (mmHg), total serum cholesterol (mmol/L), body mass index (kg/m<sup>2</sup>) and blood pressure lowering drug use (2 categories).



**Fig. 2. a** Changes in longitudinal eGFR during follow-up per one coffee cup/day increase for the total study population, and in subgroups of age, sex and smoking status, among participants of the Rotterdam Study. \* Adjusted for: age (except when stratified), sex (2 categories, except when stratified), education (4 categories), sub-cohort, smoking status (3 categories, except when stratified), physical activity, diet quality score, energy intake, alcohol- and tea consumption, systolic blood pressure, total serum cholesterol, BMI, and blood pressure lowering drug use (2 categories). Abbreviations: eGFR, estimated glomerular filtration rate; CI, confidence interval. **b** Changes in longitudinal eGFR during follow-up per one coffee cup/day increase according to subgroups of CKD risk factors, among participants of the Rotterdam Study. \* Adjusted for: age, sex (2 categories), education (4 categories), sub-cohort, smoking status (3 categories), physical activity, diet quality score, energy intake, alcohol- and tea consumption, systolic blood pressure (except when stratified by hypertension), total serum cholesterol (except when stratified by hypercholesterolemia), BMI (except when stratified) and blood pressure lowering drug use (2 categories, except when stratified by hypertension). Abbreviations: eGFR, estimated glomerular filtration rate; CI, confidence interval; T2D, type 2 diabetes; CVD, cardiovascular disease; BMI, body mass index.

In the subset of participants with additional longitudinal ACR data ( $n = 2,505$ ), 5% of the participants had ACR  $>30$  mg/g (Supplemental Table 5). Median urinary ACR did on average not change over 5.5 years of follow-up. The total number of repeated ACR measurements was 4,312 (median of 2 measurements per participant). We observed no association between coffee consumption, either continuously or in categories, and longitudinally measured log-transformed ACR during follow-up (Supplemental Table 6).

### 3.3. Coffee consumption and reduced kidney function

During 6.1 years of follow-up, 619 new cases of reduced kidney function (defined as a single measure of eGFR  $<60$  ml/min per  $1.73\text{ m}^2$  at follow-up) occurred. Although a trend towards lower risk of reduced kidney function for each additional cup of coffee per day was observed, this association was not statistically significant (Supplemental Table 7). Estimates (HRs) for categories of coffee consumption in model 3 ranged from 0.92 (0.55,1.53) for non-coffee drinkers, to 0.84 (0.66,1.06) for  $>4$  cups/day, as compared to  $>0$ –2 cups/day ( $P_{\text{trend}} = 0.07$ ).

## 4. Discussion

In this population-based cohort, coffee was not associated with longitudinally assessed eGFR and ACR in the total study population. However, among those aged  $>70$  years and/or obese participants, we found evidence of an association between higher coffee consumption and higher longitudinally assessed eGFR during follow-up, suggesting that coffee may delay kidney function decline in these subgroups. A similar trend was observed among former smokers and among those with T2D, but these associations were not statistically significant. All results were robust when non-coffee drinkers were excluded.

### 4.1. Previous studies on coffee and eGFR

Coffee's relationship with eGFR has been investigated in previous studies. In cross-sectional studies, coffee was associated with higher eGFR [28,29], or not associated [30]. However, these studies are hampered by risk of reverse causation or glomerular hyperfiltration. Glomerular hyperfiltration (i.e. functional reserve capacity) is a phenomenon which results in a temporary higher eGFR, followed by kidney function decline [31]. Both issues are less likely to occur in prospective cohort studies. To our knowledge, the Doetinchem Cohort Study is the only other study so far in which coffee and repeated assessments of eGFR have been investigated [16]. In that study, coffee was associated with slightly higher eGFR over time, but no association was found with annual eGFR change over 15 years of follow-up [16]. Interestingly, although the overall study population in their cohort was much younger, they also observed effect modification by age, with a significant association of coffee with eGFR in relatively older participants ( $\geq 46$  years), with similar effect estimates as observed in our study. Investigators of a previous MR study using data of the UK Biobank and CKDGen Consortium, also suggested that coffee beneficially affected eGFR [13]. Although pleiotropy (multiple downstream effects of a single genetic variant which affect the outcome of interest) was taken into account as much as possible, effect estimates could still have been influenced by pleiotropy in this MR study, especially because relationships between coffee variants and eGFR are likely complex. Finally, a two-week clinical trial in 19 healthy Japanese adults observed that coffee intake increased eGFR [32]. Our study adds to

this previous evidence and benefited from a large sample size, a long follow-up time, and possibilities to study various population subgroups. We observed a clear dose–response association among those aged  $>70$  years.

### 4.2. Biological mechanisms

The complex chemical composition of coffee makes it hard to unravel the underlying mechanisms that could explain the associations between coffee and higher eGFR. It is hypothesized that anti-oxidative and anti-inflammatory coffee compounds (quinides, chlorogenic acid, lignans, potassium, magnesium, niacin) play a role through improving well-established risk factors of CKD, such as blood pressure, insulin resistance and hyperglycemia [33]. Extra fluid intake (e.g. water) in heavy coffee consumers could be an alternative explanation. However, there are indications that coffee consumption does not lead to higher fluid intake [34]. Caffeine may not be responsible, as was recently suggested by a genetic study of coffee and cardiometabolic biomarkers [35]. In the aforementioned Doetinchem Cohort Study, an effect of potassium was suggested to become apparent only when people age [16]. However, coffee contains only small amounts of potassium (78 mg/100 g) [36], and its daily intake through coffee is probably too limited to fully explain the associations. Among the  $>70$  year-old participants in our study, inflammation and oxidative stress levels are probably higher as compared to these levels among younger participants [37]. As such, coffee's anti-oxidant and anti-inflammatory compounds may have played a more prominent role than potassium in the association between coffee and higher eGFR. Further, results from a recent study suggested that chlorogenic acid, which may be affected by roasting conditions, could be associated with higher risk of CKD independently from eGFR, via the benzoate metabolism pathway [38]. Further studies are needed to explore underlying pathways.

### 4.3. Coffee and eGFR in different subgroups

Our findings that higher coffee consumption was associated with higher eGFR in obese subjects, and non-significantly in T2D subjects, also support a role for inflammation and oxidative stress. Inflammation and oxidative stress levels generally increase with age and are higher in obesity and other metabolic diseases, and can thus improve more in these subgroups if they consume more coffee. Alternatively, glomerular hyperfiltration could have occurred in these higher risk groups [31]. However, we assessed eGFR in a longitudinal manner, which makes glomerular hyperfiltration less likely. Only a few studies have investigated the coffee-eGFR link in subjects with T2D or obesity. A cross-sectional study of women with and without T2D supported our findings, as a beneficial link between coffee and CKD risk was reported in those with T2D only [39]. Unlike our results and those of other studies, findings of the PREDIMED-Plus cohort suggest adverse associations between caffeinated coffee and 1-year eGFR change in obese subjects, which warrants further research on high-risk subgroups and on short versus long-term effects of coffee [40].

We also observed small differences by smoking status. Our stratified results showed larger effect estimates, although non-significant, among former smokers. This could be the result of residual confounding, e.g., former smokers may have improved their lifestyle, which could have led to an improved inflammatory response [41], subsequently leading to higher eGFR. It may also be explained by higher exposure to oxidative stress from smoking in the past, but this was not supported by our findings among current smokers, which were similar as among never smokers.

**Table 3**

Multivariable adjusted associations between coffee consumption and longitudinal eGFR in subgroups of age, sex and smoking status in 7,914 participants of the Rotterdam Study.

| Total N        |       | Total coffee consumption (cups/day) |     |      |       |                    |       |                    |       | P <sub>trend</sub> |
|----------------|-------|-------------------------------------|-----|------|-------|--------------------|-------|--------------------|-------|--------------------|
|                |       | 0                                   |     | >0-2 |       | >2-4               |       | >4                 |       |                    |
|                |       | β (95% CI)                          | N   | β    | N     | β (95% CI)         | N     | β (95% CI)         | N     |                    |
| Age (years)    |       |                                     |     |      |       |                    |       |                    |       |                    |
| ≤60            | 2,460 | 0.60 (−1.49,2.70)                   | 161 | Ref  | 492   | −1.27 (−2.57,0.03) | 906   | −1.05 (−2.41,0.32) | 901   | 0.08               |
| >60-70         | 2,927 | 1.37 (−1.58,4.32)                   | 70  | Ref  | 647   | −1.01 (−2.14,0.12) | 1,336 | −0.54 (−1.81,0.73) | 874   | 0.24               |
| >70            | 2,527 | 2.55 (−1.42,6.52)                   | 48  | Ref  | 887   | 2.85 (1.65,4.04)   | 1,181 | 3.93 (2.28,5.57)   | 411   | 0.00               |
| Sex            |       |                                     |     |      |       |                    |       |                    |       |                    |
| Men            | 3,415 | 2.05 (−0.62,4.72)                   | 97  | Ref  | 740   | 0.00 (−1.12,1.13)  | 1,408 | 0.17 (−1.06,1.39)  | 1,170 | 0.96               |
| Women          | 4,499 | 0.35 (−1.53,2.23)                   | 182 | Ref  | 1,286 | −0.01 (−0.86,0.84) | 2,015 | 0.36 (−0.69,1.40)  | 1,016 | 0.65               |
| Smoking status |       |                                     |     |      |       |                    |       |                    |       |                    |
| Never          | 2,478 | 0.73 (−1.55,3.01)                   | 133 | Ref  | 787   | 0.15 (−0.99,1.28)  | 1,087 | 0.69 (−0.76,2.13)  | 471   | 0.47               |
| Former         | 3,778 | 1.57 (−0.99,4.12)                   | 98  | Ref  | 980   | 0.36 (−0.61,1.33)  | 1,729 | 0.56 (−0.59,1.70)  | 971   | 0.38               |
| Current        | 1,658 | 0.17 (−3.61,3.95)                   | 48  | Ref  | 259   | −1.52 (−3.34,0.29) | 607   | −1.05 (−2.86,0.76) | 744   | 0.26               |

Values are regression coefficients (β) and corresponding 95% confidence intervals (95% CI) from linear mixed models of the association between coffee consumption in categories and longitudinal assessments of eGFR in ml/min per 1.73 m<sup>2</sup> during follow-up. Estimates are adjusted for age (years, except when stratified), sex (2 categories, except when stratified), education (4 categories), sub-cohort (3 categories), smoking status (3 categories, except when stratified), physical activity (MET hours/week), diet quality (score), energy intake (kcal/day), alcohol consumption (glasses/day), tea consumption (cups/day), systolic blood pressure (mmHg), total serum cholesterol (mmol/L), body mass index (kg/m<sup>2</sup>) and blood pressure lowering drug use (2 categories). Abbreviations: eGFR, estimated glomerular filtration rate; N, sample size; CI, confidence interval.

#### 4.4. Coffee and ACR

Coffee was not associated with longitudinal ACR in the current study. To our knowledge, the association between coffee and repeated measures of ACR has not been investigated before. Albuminuria as a dichotomous outcome, however, has been studied twice before [13,29]. One cross-sectional study of 342 healthy participants observed no association [29] whereas an MR study of 54,166 participants suggested a causal beneficial effect of coffee against albuminuria [13]. However, MR estimates for albuminuria were not robust, as its sensitivity analyses did not always reach statistical significance [13]. Unfortunately, our coffee-eGFR associations among

those aged >70 years and/or obese subjects could not be confirmed in ACR analyses, due to lack of statistical power.

#### 4.5. Strengths and limitations

Our study benefited from several strengths. Overall, our study had a large sample size and was community based, which improves generalizability of findings, and in which we had the opportunity to study different population subgroups. Furthermore, our study had a prospective design, which allowed us to investigate temporal associations, reducing risk for reverse causality. Also, unlike previous studies, we addressed associations of coffee with

**Table 4**

Multivariable adjusted associations between coffee consumption and longitudinal eGFR in subgroups of cardiometabolic risk factors in 7,914 participants of the Rotterdam Study.

|                          | Total N | Total coffee consumption (cups/day) |     |      |       |                    |       |                    |       | P <sub>trend</sub> |
|--------------------------|---------|-------------------------------------|-----|------|-------|--------------------|-------|--------------------|-------|--------------------|
|                          |         | 0                                   |     | >0-2 |       | >2-4               |       | >4                 |       |                    |
|                          |         | β (95% CI)                          | N   | β    | N     | β (95% CI)         | N     | β (95% CI)         | N     |                    |
| Hypertension             |         |                                     |     |      |       |                    |       |                    |       |                    |
| No                       | 2,964   | −0.45 (−2.53,1.64)                  | 129 | Ref  | 640   | −0.94 (−1.99,0.12) | 1,257 | −0.12 (−1.29,1.05) | 938   | 0.63               |
| Yes                      | 4,950   | 1.91 (−0.31,4.12)                   | 150 | Ref  | 1,386 | 0.52 (−0.37,1.41)  | 2,166 | 0.65 (−0.41,1.71)  | 1,248 | 0.24               |
| T2D                      |         |                                     |     |      |       |                    |       |                    |       |                    |
| No                       | 6,985   | 0.57 (−1.02,2.16)                   | 254 | Ref  | 1,755 | −0.16 (−0.87,0.55) | 3,037 | 0.14 (−0.68,0.96)  | 1,940 | 0.95               |
| Yes                      | 929     | 4.00 (−1.83,9.82)                   | 25  | Ref  | 271   | 1.35 (−0.93,3.63)  | 386   | 2.02 (−0.65,4.69)  | 247   | 0.15               |
| CVD                      |         |                                     |     |      |       |                    |       |                    |       |                    |
| No                       | 7,164   | 0.82 (−0.77,2.40)                   | 258 | Ref  | 1,796 | −0.15 (−0.86,0.56) | 3,105 | 0.19 (−0.63,1.00)  | 2,005 | 0.89               |
| Yes                      | 751     | 2.22 (−4.47,8.91)                   | 21  | Ref  | 230   | 0.38 (−2.15,2.91)  | 319   | 0.58 (−2.56,3.72)  | 181   | 0.75               |
| Hypercholesterolemia     |         |                                     |     |      |       |                    |       |                    |       |                    |
| No                       | 4,967   | 1.12 (−0.81,3.06)                   | 172 | Ref  | 1,241 | 0.01 (−0.85,0.88)  | 2,174 | 0.50 (−0.49,1.50)  | 1,380 | 0.48               |
| Yes                      | 2,947   | 0.82 (−1.78,3.41)                   | 107 | Ref  | 785   | −0.15 (−1.30,1.01) | 1,250 | −0.08 (−1.44,1.30) | 805   | 0.81               |
| BMI (kg/m <sup>2</sup> ) |         |                                     |     |      |       |                    |       |                    |       |                    |
| ≤25                      | 2,535   | 0.83 (−1.70,3.36)                   | 106 | Ref  | 675   | −0.00 (−1.19,1.19) | 1,066 | 0.21 (−1.18,1.60)  | 688   | 0.86               |
| >25-30                   | 3,718   | 0.26 (−2.05,2.57)                   | 124 | Ref  | 942   | −0.57 (−1.56,0.42) | 1,647 | −0.38 (−1.53,0.76) | 1005  | 0.36               |
| >30                      | 1,661   | 3.18 (−0.62,6.97)                   | 49  | Ref  | 409   | 1.18 (−0.43,2.79)  | 710   | 1.70 (−0.11,3.51)  | 493   | 0.08               |

Values are regression coefficients (β) and corresponding 95% confidence intervals (95% CI) from linear mixed models of the association between coffee consumption in categories and longitudinal assessments of eGFR in ml/min per 1.73 m<sup>2</sup> during follow-up. Estimates are adjusted for age (years), sex (2 categories), education (4 categories), sub-cohort (3 categories), smoking status (3 categories), physical activity (MET hours/week), diet quality (score), energy intake (kcal/day), alcohol consumption (glasses/day), tea consumption (cups/day), SBP (mmHg, except when stratified by hypertension), total serum cholesterol (mmol/L, except when stratified by hypercholesterolemia), BMI (kg/m<sup>2</sup>, except when stratified) and blood pressure lowering drug use (2 categories, except when stratified by hypertension). Hypertension is present in case of SBP ≥140 mmHg or DBP ≥90 mmHg and/or blood pressure lowering drug use. T2D is present in case of self-reported physician's diagnosis, use of glucose lowering drugs, or elevated plasma glucose level (≥7 mmol/L if fasted for ≥4 h or ≥11.1 mmol/L if not fasted). CVD is defined as coronary heart disease and/or stroke. Hypercholesterolemia is defined as total serum cholesterol ≥6.5 mmol/L and/or lipid reducing drug use. Abbreviations: eGFR, estimated glomerular filtration rate; N, sample size; T2D, type 2 diabetes; CVD, cardiovascular disease; BMI, body mass index; CI, confidence interval; SBP, systolic blood pressure; DBP, diastolic blood pressure.

ACR over time. Limitations include that coffee was self-reported, which could have led to non-differential misclassification, and underestimation of results. Furthermore, longitudinal urinary ACR measurements were available for only part of the study population. Although results for ACR were in line with results of longitudinal eGFR analyses in the overall population, we lacked power to determine associations with ACR in subgroups (i.e., 70+ aged and obese subjects). We also acknowledge that, although this study was population-based, it only included participants aged >45 years which hampers generalizability to younger participants. Also, we measured coffee and dietary covariates at baseline only, not potential changes in dietary habits. Although previous studies in Dutch elderly have shown relatively stable dietary patterns over time [42], we may speculate that those with higher disease risk, among whom we observed strongest associations, may have been more likely to have changed their diet or coffee intake over time. Finally, coffee additives (sugar, milk, cream) were not considered, but we adjusted for several confounders, including a measure of overall diet quality. Still, as in every observational study, residual confounding cannot be excluded.

## 5. Conclusion

Although in the total study population we did not find evidence of an association between coffee and longitudinal eGFR or ACR during follow-up, results suggest that higher coffee intake may help to preserve eGFR among CKD risk groups. We observed beneficial associations of coffee with delayed kidney function decline for those aged >70 years and obese participants. Similar trends were observed in those with T2D, and to lesser extent, in former smokers. These findings in high-risk subgroups require further investigation and replication in other prospective cohort studies first, before being translated to clinical practice.

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## Author contribution

**ACvW:** conceptualization, methodology, software, formal analysis, investigation, writing – original draft, visualization **COR:** conceptualization, methodology, software, writing-review & editing, supervision **ACvdB:** writing-review & editing **LC:** writing-review & editing **JMG:** writing-review & editing **EJH:** writing-review & editing **TV:** conceptualization, methodology, writing-review & editing, supervision. Each author contributed important intellectual content during manuscript drafting or revision and agrees to be personally accountable for the individual's own contributions and to ensure that questions pertaining to the accuracy or integrity of any portion of the work, even one in which the author was not directly involved, are appropriately investigated and resolved, including with documentation in the literature if appropriate.

## Conflict of interest

All authors declare they have no conflict of interest relevant to the content of this article.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.clnu.2022.11.017>.

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