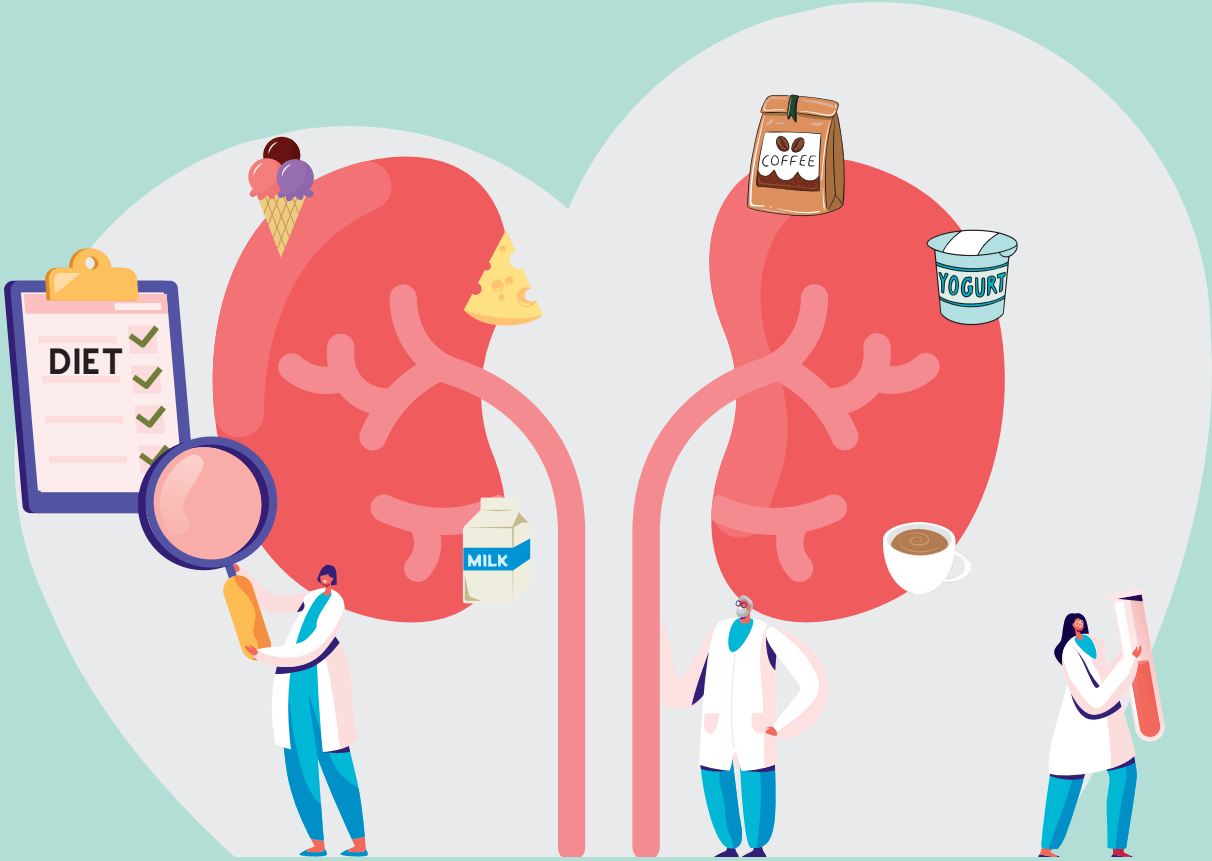
Nutrition and kidney function:
prospective studies in healthy participants and cardiovascular patients

Anniek C. van Westing



Propositions

1. Dietary guidelines for the prevention of chronic kidney disease in healthy individuals do not apply to cardiovascular patients.
   (this thesis)

2. Coffee should be part of a kidney-friendly diet, particularly for diabetes patients.
   (this thesis)

3. Journals should incorporate peer review of statistical analysis codes to ensure the integrity of published papers.

4. The COVID-19 pandemic adversely affected the visibility and social development of PhD students.

5. Online study programs promote a sedentary lifestyle and lazy attitude amongst students.

6. Tennis is an underrated strategy for improving mental health.

Propositions belonging to the thesis, entitled

Nutrition and kidney function: prospective studies in general populations and cardiovascular patients

Anniek C. van Westing
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Nutrition and kidney function:

prospective studies in healthy participants and cardiovascular patients

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Thesis

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Chapter 1

General introduction

This thesis aims to investigate the role of nutritional factors in relation to parameters of kidney function decline using observational data of: (i) general populations, and (ii) cardiovascular disease (CVD) patients. It also investigates these associations in subgroups at higher risk of chronic kidney disease (CKD), such as those with diabetes mellitus, hypertension, and obesity. The nutritional factors studied include overall dietary intake, diet quality, and blood biomarkers. The first part of this chapter presents the burden of CKD, its bidirectional association with CVD, and the link with non-alcoholic fatty liver disease (NAFLD). It also provides the readers with general information on kidney function assessment, classification of CKD, and age-related kidney function decline. In the 2nd part, the importance of a healthy diet for slowing down kidney function decline is explained, as well as the role of blood biomarkers (including n-3, n-6 fatty acids [FAs] and serum uric acid [SUA]) in the early detection of patients at high risk of CKD. In the final part, the objectives and outline of this thesis are described.

Chronic kidney disease and kidney function

The burden of chronic kidney disease and cardiovascular disease

CKD is a progressive condition characterised by a gradual kidney function decline over time. With an estimated global prevalence of 9% in 2017, CKD has become a major public health problem (1). CKD is strongly associated with a range of diseases, including kidney failure and CVD. With 1.2 million deaths globally in 2017, CKD is also strongly associated with premature death (1). In 2040, CKD is expected to be the 5th cause of death worldwide, after ischemic heart disease, stroke, lower respiratory infections, and chronic obstructive pulmonary disease (2). In the Netherlands, about one in ten adults has CKD, which translates to 1.7 million people (3). A large proportion of these patients may not be aware of the fact that they have the condition, because the disease is largely asymptomatic, and patients start having complaints (i.e., itch, fatigue, nausea, lack of appetite), only in the more advanced stages of CKD (4). The prevalence of CKD is expected to continue to rise, because of the increase in CKD's primary risk factors including aging, obesity, diabetes and hypertension (1, 5, 6). Other important risk factors of CKD are smoking and history of CVD (7).

In 2021, CVD mortality accounted for 22% of all deaths in the Netherlands (8). A large proportion of CVD patients have CKD, because of their accelerated kidney function decline (9). For example, in CVD patients of the EUROASPIRE IV survey of the European Society of Cardiology, the CKD prevalence was 20% (10). At the same time, CVD is the primary cause of death in CKD patients, rather than kidney failure (6). This is also referred to as the cardiorenal syndrome, in which dysfunction of the heart leads to dysfunction of the kidneys and vice versa (11). CKD and CVD share several cardiovascular risk factors including, but not limited to, diabetes, hypertension, dyslipidaemia, and smoking (6). However, two meta-analyses have shown that CKD also elevates cardiovascular risk independent of hypertension and diabetes

(12, 13). Two other underlying mechanisms of this pathological interplay include chronic inflammation and activation of renin-angiotensin aldosterone system (RAAS) (11).

Non-alcoholic fatty liver disease

Just like CKD, NAFLD has become an increasing public health problem worldwide, and this disorder is expected to rise over the next decades (14-16). NAFLD is a term used to describe a range of liver conditions that are not caused by excessive alcohol consumption and other competing causes of liver disease. NAFLD is characterised by the accumulation of fat in the liver cells, and is preferably diagnosed with ultrasonography in clinical practice (17). Large observational cohort studies often use the Fatty Liver Index (FLI) to predict NAFLD. The FLI is a valid scoring system based on BMI, waist circumference, gamma glutamyl-transferase, and triglycerides (18). NAFLD is strongly associated with obesity and type 2 diabetes (15). Also the link with CKD has been well documented since the last decade (19-21), with an increasing prevalence of CKD in patients with NAFLD in recent years (22). Notably, after adjusting for independent risk factors of CKD, the association between NAFLD and CKD persisted. The early stages of NAFLD are reversible and treatment often involves lifestyle changes, such as losing weight, adopting a healthier diet, and increasing physical activity (15). Without proper treatment, NAFLD can progress to liver failure, which is an irreversible disease stage. Apart from CKD, NAFLD is also associated with other extra-hepatic complications, such as CVD (23). It is therefore of interest to also study the relationship of NAFLD and CKD in CVD patients.

Kidney function assessment and classification of chronic kidney disease

CKD is defined as abnormalities of kidney function or structure, present for >3 months, according to guidelines from Kidney Disease: Improving Global Outcomes (KDIGO) (24). The diagnosis of CKD is largely based on glomerular filtration rate (GFR), and in some cases supplemented with information about albuminuria. GFR is a measure of kidney function. It can be measured directly (mGFR) using inulin (the gold standard), but this method is expensive and invasive for the patient (25, 26). In clinical practice, GFR is estimated (eGFR) using the measurement of endogenous filtration markers, i.e., serum creatinine and/or serum cystatin C (27, 28). In accordance with KDIGO clinical practice guidelines, the creatinine-based equation of the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) is then used to estimate GFR (24, 29). The CKD-EPI Collaboration also developed an equation including serum cystatin C only (30), both serum creatinine and serum cystatin C (30), and most recently, a version without a race variable (31). Previous research has shown that the combined serum creatinine-cystatin C CKD-EPI equation performs better than either of the markers alone (30). The 2009 creatinine CKD-EPI formula, and the combined creatinine-cystatin C CKD-EPI formula from 2012 (with race) and 2021 (without race) are shown below in **box 1**.

Box 1. An overview of CKD-EPI equations

2009, creatinine only (29)

$$eGFR_{cr} = 141 \cdot \min\left(\frac{Scr}{\kappa}, 1\right)^{\alpha} \cdot \max\left(\frac{Scr}{\kappa}, 1\right)^{-1.209} \cdot 0.993^{Age} [\cdot\ 1.018\ if\ female][\cdot\ 1.159\ if\ black]$$

S_{cr} = serum creatinine
κ = 0.7 (females) and 0.9 (males)
α = −0.329 (females) and −0.411 (males)
min = the minimum of Scr/κ or 1
max = the maximum of Scr/κ or 1

2012, combined creatinine and cystatin C, with race (30)

$$eGFR_{cr-cys} = 135 \cdot \min\left(\frac{Scr}{\kappa}, 1\right)^{\alpha} \cdot \max\left(\frac{Scr}{\kappa}, 1\right)^{-0.601} \cdot min\left(\frac{Scys}{0.8}, 1\right)^{-0.375} \cdot \left(\frac{Scys}{0.8}, 1\right)^{-0.711} \cdot 0.995^{Age} [\cdot\ 0.969\ if\ female\ ][\cdot\ 1.08\ if\ black]$$

S_{cr} = serum creatinine
S_{cys} = serum cystatin C
κ = 0.7 (females) and 0.9 (males)
α = −0.248 (females) and −0.207 (males)
min = the minimum of Scr/κ or 1
max = the maximum of Scr/κ or 1

2021, combined creatinine and cystatin C, without race (31)

$$eGFR_{cr-cys} = 135 \cdot \min\left(\frac{Scr}{\kappa}, 1\right)^{\alpha} \cdot \max\left(\frac{Scr}{\kappa}, 1\right)^{-0.544} \cdot min\left(\frac{Scys}{0.8}, 1\right)^{-0.323} \cdot \left(\frac{Scys}{0.8}, 1\right)^{-0.778} \cdot 0.9961^{Age} \cdot 0.963\ [if\ female]$$

S_{cr} = serum creatinine
S_{cys} = serum cystatin C
κ = 0.7 (females) or 0.9 (males)
α = -0.219 (females) or -0.144 (males)
min = the minimum of Scr/κ or 1
max = the maximum of Scr/κ or 1

Albuminuria can be measured using the urinary albumin-to-creatinine ratio (ACR), and it provides information about anatomical or structural abnormalities in the kidneys (24). Where one of the main functions of the kidneys is to filter waste products (metabolic products, toxins, ions) (32) from the blood and reabsorb proteins back in the blood, damaged kidneys are less able to do so, which results in leakage of proteins in the urine. Albuminuria is a pivotal indicator of kidney function loss, a strong predictor of CVD mortality, and is already present in early stages of CKD when the kidney function is still normal (7, 24). Other important functions of the kidneys are 1) regulation of blood pressure via the RAAS 2) maintaining water,

electrolyte, and acid-base homeostasis, and 3) production and metabolism of hormones, such as vitamin D (32). In CKD patients, lower levels of active serum 1,25-dihydroxy-vitamin D (i.e., 1,25[OH_2]D) contribute to higher risk of bone disorders (33). CKD severity is classified in five stages based on eGFR, ranging from stage G1 (normal or high, eGFR ≥90 mL/min per 1.73 m^2) to stage G5 (kidney failure, eGFR <15 mL/min per 1.73 m^2) (24). Stage G5, i.e., kidney failure, is associated with poor quality of life and increased morbidity and mortality (5, 24). Treatment options are dialysis or kidney transplant (24). Albuminuria severity stages range between A1 (normal to mildly increased, <30 mg/g) to A3 (severely increased, >300 mg/g) (24). The prognosis of CKD is largely based on the combination of eGFR and albuminuria, with the highest risk of kidney failure and CVD in patients with CKD stages >G3a and albuminuria stages ≥A3 (24). In research and clinical practice, CKD is commonly defined as eGFR <60 mL/min per 1.73 m^2 (24). The stages of CKD severity and albuminuria, and prognosis, are presented in **Fig. 1**.

Prognosis of CKD by GFR and Albuminuria Categories: KDIGO 2012

GFR categories (ml/min/ 1.73 m^2) Description and range				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol
	G1	Normal or high	≥90			
	G2	Mildly decreased	60-89			
	G3a	Mildly to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	<15			

Fig. 1 Stages of CKD and albuminuria, and associated risk of kidney failure and CVD. Green: low risk (if no other markers of kidney disease, no CKD); yellow: moderately increased risk; orange: high risk; red: very high risk. Adapted from KDIGO guidelines (24). CKD, chronic kidney disease; GFR, glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes.

The aging kidney and age-related kidney function decline

Aging is the main contributor to chronic diseases (34), including CVD and CKD. A normal aging kidney is characterised by anatomical and functional changes, i.e., the kidneys have decreased

in size, volume and cortex (35), and there is an increase in incidence of glomerulosclerosis, tubulo-interstitial fibrosis, and renal atherosclerosis (36). Glomerular filtration occurs in the nephrons, which are the functional units of the kidney (32). Aging of the kidneys result in nephron loss and nephrosclerosis, and this will ultimately result in lower eGFR (36). The average age-related kidney function decline in healthy populations ranges between 0.8-1.0 mL/min per 1.73 m^2 per year probably starting in someone's mid-30s (37, 38), but comorbidities, such as diabetes, obesity, NAFLD, and CVD can accelerate this decline (9, 37, 39, 40). CVD patients in particular, have accelerated kidney function decline, estimated to be twice as fast as healthy persons, leading to a higher risk of CKD (9).

Box 2. Raising awareness of kidney damage

Currently, the public awareness of maintaining healthy kidneys is low (41). Given the high mortality and morbidity rates, prevention of CKD (progression) or delaying kidney function decline is highly important and should be a call for action, particularly in vulnerable subgroups such as those with CVD. However, CKD as public health problem and as problem for patients with CVD, is currently not a high priority for many health authorities.

Diet as modifiable risk factor

It is well established that a healthy lifestyle, which also includes a high quality diet, is important for the primary prevention of CVD (42). Analyses in various cohort studies in both well and less well-treated CVD patients have also shown the importance of a high quality diet for secondary prevention (43-48). CKD and CVD share common risk factors, and thus a better diet quality may also prevent CKD or delay kidney function decline in both the primary and secondary context. The role of a healthy diet to prevent CKD progression or (CVD) mortality was recently examined in a US cohort of established CKD patients (49). In the context of secondary prevention, a healthy and high quality diet may also prevent CKD in the growing CVD population who are largely treated with lipid-lowering drugs and antihypertensive medication. The Dutch Health Council defined dietary guidelines for the general population in 2015 (50), and re-evaluated these guidelines for patients with CVD in 2023 (51). These guidelines and the recommendation for a healthy BMI and daily energy intake, are listed in **box 3**. In addition to lifestyle and diet, also genetics is an important determinant for kidney function decline. In a recent trans-ancestry genome-wide association study (GWAS) meta-analysis for kidney function, 308 single nucleotide polymorphisms (SNPs) explained about 7% of the variability in eGFR (52). Genetics could reveal insight in mechanisms underlying kidney function decline in health and disease, which could then provide opportunities for therapeutic targets. Specifically, a genetic risk score (GRS) which summarises the genetic profile of a person across the identified genetic variants, is helpful for this purpose.

Box 3. Guidelines for diet quality, daily energy intake, and healthy body weight

Dutch dietary guidelines 2015 for the general population (adapted from (57))

- Consume ≥200 grams/day of vegetables
- Consume ≥200 grams/day of fruit
- Consume ≥90 grams/day of wholegrain products, and replace refined cereal products by wholegrain products
- Consume legumes weekly
- Consume ≥15 grams/day of unsalted nuts
- Consume a few portions of dairy products daily, including milk or yogurt
- Consume 1 portion of fish weekly, preferably fatty fish
- Drink three cups/day of green or black tea
- Replace butter, hard margarines and cooking fats by soft margarines, liquid cooking fats and vegetable oils
- Replace unfiltered coffee by filtered coffee
- Limit the consumption of red meat
- Limit the consumption of processed meat
- Limit the consumption of sweetened beverages and fruit juices
- If alcohol is consumed at all, intake should be limited to one Dutch unit (10 grams/day ethanol)
- Limit the consumption of table salt to 6 grams/day

Dutch dietary guidelines 2023 for CVD patients (adapted from (51))

The recommendations for CVD patients are similar to the dietary guidelines for the general population, except for fish. For CVD patients, the recommendation is to consume 1-2 portions of (fatty or lean) fish per week. In addition, the dietary guidelines also include the recommendation to consider the use of products enriched with plant sterols or stanols, on doctor's advice.

Guidelines for daily energy intake and a healthy body-weight

- In healthy populations, the recommended daily energy intake for adults is 2000 kilocalories for women and 2500 kilocalories for men, depending on age and level of physical activity (adapted from (58)). In CVD patients, however, energy needs likely differ, but this is understudied (58).
- In healthy populations, accepted measures of a healthy body weight include a BMI between 18.5-25 kg/m^2 and a waist circumference <94 cm in men and <80 cm in women (adapted from (59)). In CVD patients, however, a healthy BMI of 25-30 kg/m^2 is considered acceptable (60).

Previous population-based studies have mainly focused on adherence to healthy dietary patterns such as the Dietary Approaches to Stop Hypertension diet and Mediterranean diet in relation to various kidney function parameters (53). Also in the context of secondary prevention, effects of adherence to a Mediterranean diet vs low-fat diet on kidney function decline have been investigated (54). However, knowledge on the association between diet quality for CVD patients and kidney function, and the potential interaction with genetics is lacking.

Personalised nutrition for cardiovascular disease patients

Personalised nutrition refers to tailoring dietary recommendations to an individual's specific needs, taking into account factors such as nutritional status, current health status (phenotype), and genetic makeup (55). Genetic factors in CVD patients, in combination with nutrition and other lifestyle factors, can influence the risk and progression of diseases, including CKD (56). To identify CVD patients at high risk of developing CKD, a GRS for CKD may be useful. Patients with a high genetic risk of CKD may respond differently to dietary factors compared to those with a low genetic risk. Incorporating the GRS for CKD into personalised nutrition strategies could offer healthcare providers possibilities for targeted dietary recommendations specifically designed for CVD patients.

Growing interest in coffee and dairy for chronic kidney disease prevention

Within these healthy and high quality diets, there is also a growing interest in specific beverages and foods that may explain beneficial associations with CKD. Coffee in particular is a popular research topic in the field of cardiometabolic diseases. Previous studies in healthy populations have shown potential protective effects of coffee against type 2 diabetes (61, 62) and hypertension (63), the primary risk factors of CKD. Researchers have also shown increasing interest in dairy products as a beneficial food group for preventing CKD (64), which they attributed to blood pressure lowering minerals and/or anti-inflammatory nutrients (65, 66). Coffee and dairy are further outlined below in relation to kidney function.

Coffee

With ≥2 billion cups/day, coffee is the most widely consumed beverage worldwide (67), together with tea and water. Therefore, small physiological effects may have major public health implications. A recent review showed that coffee consumption is associated with reduced risk of various cardiovascular outcomes (68). Given the body of evidence available for type 2 diabetes (61, 62) and hypertension (63), coffee may also protect against CKD. Indeed an abundance of studies in largely healthy populations is available on potential protective effects of coffee against incident CKD, kidney failure, and albuminuria (69-73). However, research is limited and inconsistent on associations of coffee with kidney function decline (74, 75) and there are no studies on coffee and albuminuria over time. Research is also limited in vulnerable subgroups. To date, only one study so far has been performed

among Japanese type 2 diabetes patients of the Fukuoka Diabetes Registry, showing potential favourable effects of coffee against kidney function decline (76). However, Japanese people consume more (green) tea than coffee, so it is important to study the potential protective effects of coffee on eGFR in populations with high coffee consumption. Prevention of CKD and albuminuria is important, but monitoring (long-term) changes in kidney function (eGFR) and kidney damage (albuminuria) as a consequence of habitual coffee consumption, is equally important.

Dairy

In addition to coffee, dairy has also been suggested to affect kidney health, particularly low-fat dairy (64). Just like coffee, dairy is a major contributor of the Dutch diet, so small effects may have large public health implications. In population-based studies, full-fat dairy was not associated with kidney function outcomes (77-79). Dairy is a heterogenous food matrix, consisting of micronutrients (i.e., calcium, potassium, magnesium) and macronutrients (i.e., protein and mainly saturated fatty acids and *trans* fatty acids), which may exert opposing effects on kidney health. Furthermore, various dairy products differ in calories, nutrient density, and level of processing. The majority of previous studies focused on associations between total dairy, including low-fat dairy, and kidney function outcomes in generally healthy populations (64). Data on associations of dairy with kidney outcomes in CVD patients are lacking, and studies on specific dairy products in relation to kidney function decline in CVD patients are warranted.

Blood biomarkers

In clinical practice, biomarkers may be useful for screening, diagnosis, and monitoring of diseases, including CKD. Key biomarkers of kidney function are serum creatinine and serum cystatin C, on basis of which eGFR can be assessed to classify the stage of CKD (24). Higher levels of serum uric acid (SUA) may also be used as indicator of the presence of CKD, since uric acid is mainly excreted by well-functioning kidneys. Uric acid is an end-product of purine metabolism and could be linked to the consumption of purine-rich diets (a diet rich in red meat, fatty poultry, full-fat dairy, seafood products and alcohol) (80). A high-fructose diet may also increase the levels of SUA (81). SUA could be used as biomarker for risk assessment, because of the association with premature mortality in various populations (82). Related to SUA, plasma FAs such as linoleic acid (LA, an omega-6 FA), eicosapentaenoic (EPA), docosahexaenoic (DHA, both n-3 FAs), and odd-chain FAs (i.e., C15:0 and C17:0) may also be of interest for kidney function decline, because of their correlation with diet (83-86). Identifying biomarkers of accelerated kidney function decline provide opportunities for treatments to slow down kidney function decline. If the nutritional biomarkers are located on the causal pathway, this will likely result in improved life expectancy. A previous analysis of CVD patients

of the Alpha Omega Cohort found a 2-3-fold higher risk of CVD mortality for patients with an eGFR of 30-59 vs eGFR >90 mL/min per 1.73 m^2. In CVD patients with eGFR <30 mL/min per 1.73 m^2, the risk of premature death from CVD was 4-6-fold higher (87). The results of this study argue for the need to search for biomarkers, which could help identify CVD patients at higher risk of accelerated kidney function decline.

Plasma fatty acids

Circulating levels of FAs in the blood may be considered as objective biomarkers of FA intake (88). In the Alpha Omega Cohort, circulating EPA and DHA were moderately correlated with dietary intake of these FAs (*r* of 0.4-0.5), whereas only a weak correlation was found for plasma vs dietary LA (*r* of 0.1-0.2) (89). Circulating FAs have been linked to cardiometabolic health in multiple studies (84, 90-96). EPA and DHA, as markers of fish or fish fatty acid intake, have been associated with a lower CVD risk, also in the Alpha Omega Cohort (97). Plasma odd-chain FAs (OCFAs), as markers of dairy intake, have also been associated with a lower CVD risk in population-based studies (98). The role of C14:0, also known as myristic acid and commonly found in dairy, coconut or palm oil, in cardiometabolic diseases remains unclear (99, 100). Data on plasma FAs and kidney function decline are scarce in population-based studies (101, 102), and lacking in CVD patients. Studies are warranted to investigate whether these FAs could function as biomarker of kidney function decline in CVD patients.

Serum uric acid

Uric acid is produced by the liver and primarily excreted by the kidneys (103), and may therefore be linked to NAFLD (104) and CKD (105). Indeed, a disbalance in the production and excretion of SUA is observed in patients with CKD and/or NAFLD, which eventually results in elevated SUA levels (104, 105). Elevated SUA levels are associated with increased risk of various health complications, including CKD (106). In CVD patients of the Alpha Omega Cohort, CKD and NAFLD predicted by FLI, have each been associated with higher risk of (CVD) mortality (87, 107). Studying SUA as biomarker of NAFLD and CKD, and as predictor of long-term mortality, may provide clinical practice with a useful, inexpensive tool for risk assessment.

Objectives and outline of this thesis

To what extent a healthy diet could slow down kidney function decline among patients with established CVD is not yet clear. Blood biomarkers may be useful when studying nutritional factors and cardiometabolic health, but little is known about their relation with kidney function in CVD patients. Relationships of dietary factors and biomarkers with CKD may be impacted by medication use, underlying disease processes and genetic risk, but these interactions have not been extensively studied in CVD patients.

Box 4. The main objectives

The **main objectives** of this thesis are to investigate associations of nutritional factors with parameters of kidney function decline in general populations and stable CVD patients. Both dietary factors and blood biomarkers were studied. For dietary factors, I focused on overall dietary intake, diet quality, and on coffee and dairy in particular, which could all be important for CKD prevention. For blood biomarkers, I focused on nutritional biomarkers LA, EPA+DHA, OCFAs, and C14:0, which could also be important for CKD prevention. Additionally, I studied SUA, because of potential value as a blood biomarker for risk assessment in stable CVD patients.

Study designs

Four chapters in this thesis are based on data of the Alpha Omega Cohort. The Alpha Omega Cohort consists of 4837 Dutch post-MI patients (aged 60-80 years, 78% male) with a verified history of MI ≤10 years before study enrolment (108, 109). Most patients used state-of-the-art cardiovascular medication, including antihypertensive drugs and statins. At baseline (2002-2006), data on demographic factors, habitual diet (validated food frequency questionnaire), lifestyle (questionnaire), medical history and medication use, CVD risk factors and biomarkers in blood were collected (108). Data on kidney function (eGFR, CKD-EPI equation) were collected at baseline and after ~40 months of follow-up. Patients have been continuously monitored for cause-specific mortality through 31 December 2018.

The thesis also includes data from the **Rotterdam Study (RS)**. The RS is an ongoing population-based cohort study in the district Ommoord, Rotterdam, the Netherlands. The main aim of this cohort is to investigate etiology, preclinical course, natural history and potential targets for intervention for chronic diseases in mid-life and late-life (110). In total, 14,926 healthy adults aged ≥45 years were enrolled in the RS. Data collection was conducted on demographic factors, habitual diet (validated food frequency questionnaires (FFQ) (111-113) and home interviews), lifestyle (self-reported questionnaire), medical history and medication use (pharmacy records and home interviews), CVD risk factors, and biomarkers in urine and blood. Creatinine-based eGFR (CKD-EPI equation) and albuminuria (ACR) were calculated at baseline and various follow-up visits. Data of the **Lifelines Cohort Study** are also included in this thesis. The Lifelines Cohort Study is an ongoing population-based cohort study, which aims to examine health and health-related behaviours of 167,729 generally healthy adults living in three provinces of Northern Netherlands. Baseline measurements took place in 2006-2011, and the first follow-up investigation of all participants was performed during the period 2014-2019. Data collection at baseline and follow-up included sociodemographic factors (self-reported questionnaires), habitual diet (validated FFQ (114)), lifestyle (self-reported questionnaire), biomarkers in blood, eGFR (CKD-EPI equation) and other CVD risk factors, medication use and medical history.

Outline of the thesis

Fig. 2 presents the outline of this thesis, which is divided into three parts. Part A (Chapters 2 and 3) describes the role of diet on kidney function. In part B (Chapters 4, 5 and 6), I present results of studies on coffee and dairy products in relation to kidney function decline. Studies on blood biomarkers in relation to kidney function decline, NAFLD, and long-term mortality are presented in part C (Chapters 7 and 8).

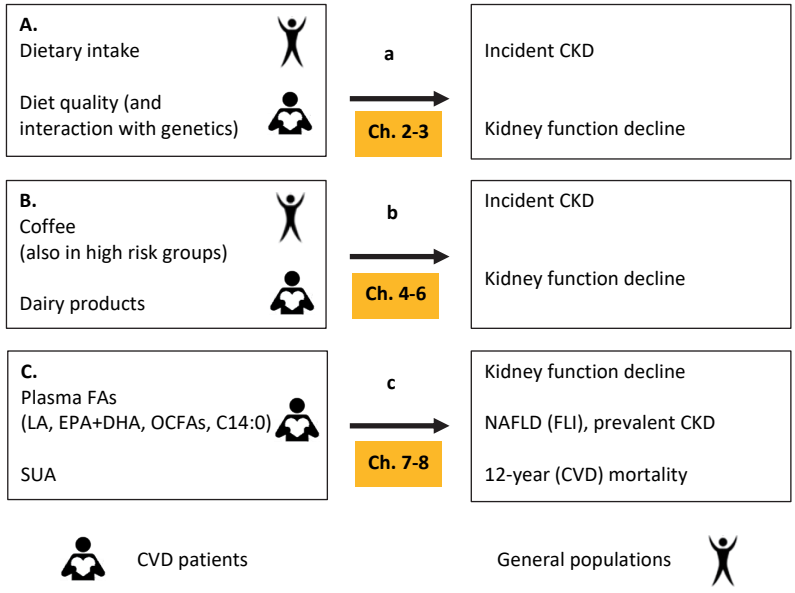

Fig. 2 Outline of the thesis. CKD, chronic kidney disease; FAs, fatty acids; OCFA, odd-chain fatty acids; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; LA, linoleic acid; SUA, serum uric acid; NAFLD, non-alcoholic fatty liver disease; FLI, fatty liver index; CVD, cardiovascular disease.

The black arrows represent the specific objectives:

a) To investigate relationships of overall dietary intake and diet quality with kidney function decline in general populations and stable CVD patients. For diet quality among CVD patients, I additionally examined effect modification by genetic risk of CKD (Chapters 2-3).

b) To examine associations for coffee and dairy in relation to kidney function decline in general populations (coffee) and CVD patients (dairy). Associations for coffee were investigated in more detail in various vulnerable subgroups with CKD risk factors (Chapters 4-6).

c) To study relationships of blood biomarkers with kidney function decline, prevalent CKD, NAFLD and (CVD)-mortality in stable CVD patients. Also here, relationships were investigated in various subgroups with CKD risk factors. Additionally, the diagnostic utility of SUA as biomarker of NAFLD and CKD was investigated, using sensitivity and specificity analysis (Chapters 7-8).

In **Chapter 2**, the current state of knowledge regarding the potential influence of commonly consumed foods, drinks, and dietary patterns on various kidney function outcomes in general populations is presented in the form of a literature review. In **Chapter 3**, the association between diet quality and kidney function decline among CVD patients is examined. In addition, the potential interaction between diet quality and genetic risk of CKD is further investigated by means of a GRS for CKD. In **Chapters 4 and 5**, results from studies on the association between habitual coffee consumption and kidney function decline in ~8000 participants of the RS (Chapter 4) and ~78,000 participants of the Lifelines Cohort Study (Chapter 5) are presented. Additionally, the association between coffee consumption and kidney function decline in various vulnerable subgroups (those with CKD risk factors, i.e., older age, hypertension, diabetes, obesity, etc.) is assessed in both chapters. In Chapter 4, also albuminuria is investigated as an outcome. In **Chapter 6**, the association between popular dairy products and kidney function decline among Dutch post-MI patients of the Alpha Omega Cohort is described. **Chapter 7** explores whether various plasma FAs (LA, EPA, DHA, OCFAs and C14:0) could function as biomarker of kidney function decline in the Alpha Omega Cohort. The cross-sectional association between FLI as validated predictor of NAFLD, and CKD among patients of the Alpha Omega Cohort is studied in **Chapter 8**. Furthermore, the diagnostic performance of SUA to detect the (combined) presence and absence of NAFLD and CKD is evaluated, including the association between SUA (as biomarker of NAFLD and CKD) and 12-year (CVD) mortality risk.

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Part A

Diet quality and kidney function

Chapter 2

Diet and kidney function: a literature review

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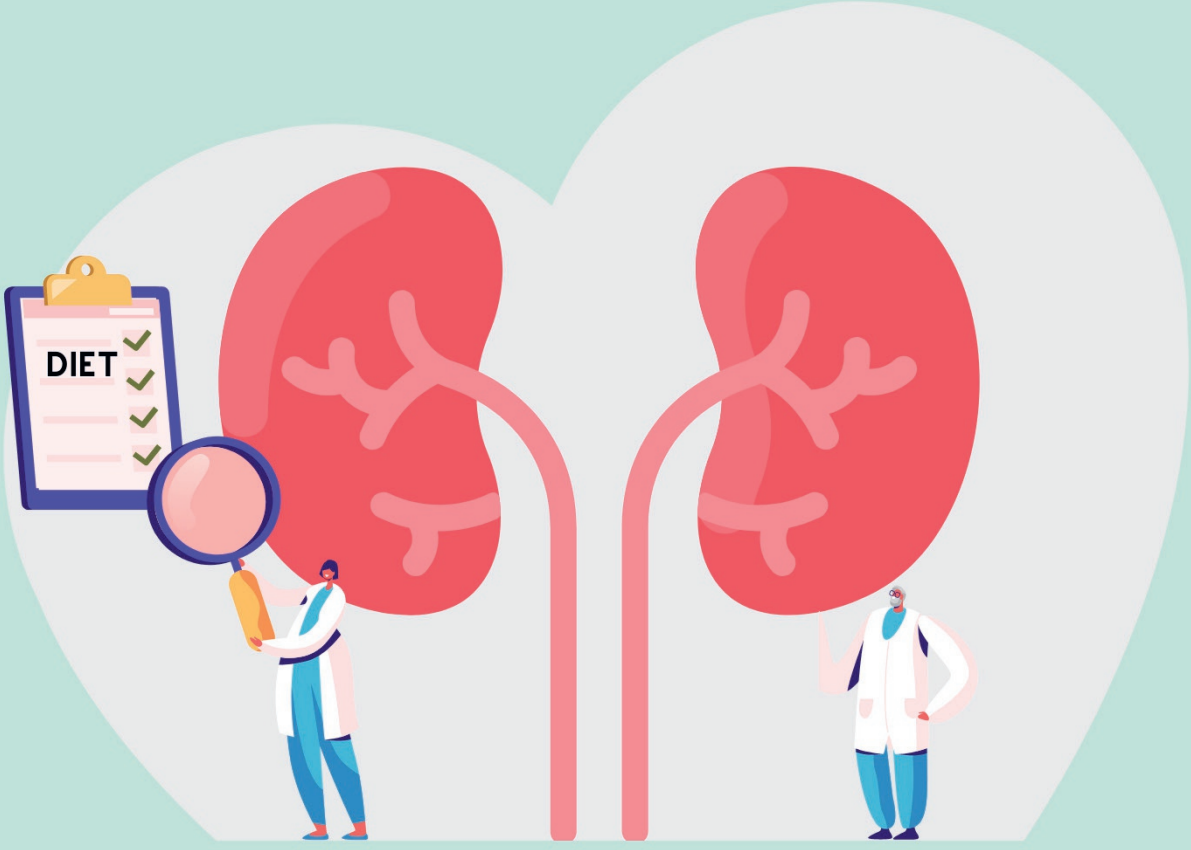

Abstract

Purpose of review The burden of chronic kidney disease (CKD) is increasing worldwide. For CKD prevention, it is important to gain insight in commonly consumed foods and beverages in relation to kidney function.

Recent findings We included 21 papers of prospective cohort studies with 3–24 years of follow-up. We focused on meat, fish, dairy, vegetables, fruit, coffee, tea, soft drinks, and dietary patterns. There was convincing evidence that a healthy dietary pattern may lower CKD risk. Plant-based foods, coffee, and dairy may be beneficial. Unhealthy diets and their components, such as red (processed) meat and sugar-sweetened beverages, may promote kidney function loss. For other foods and beverages, associations with CKD were neutral and/or the number of studies was too limited to draw conclusions.

Summary Healthy dietary patterns are associated with a lower risk of CKD. More research is needed into the effects of specific food groups and beverages on kidney function.

Introduction

Chronic kidney disease (CKD) is a major public health burden (1, 2), with a global prevalence of ~11% in the general adult population (1). If left untreated, CKD slowly progresses to end-stage renal disease, which requires dialysis or kidney transplant (2, 3). CKD is bidirectionally associated with cardiovascular diseases (CVD) (4, 5). Hypertension (6) and type 2 diabetes mellitus (T2DM) (7, 8) are independent risk factors for CKD (6, 7), and their global prevalences are increasing (9, 10), which will likely impact CKD. Worldwide, a 31.7% increase of CKD mortality was observed over the last decade (11).

Lifestyle factors, including smoking (12), alcohol use (13), and physical inactivity (14), could promote CKD. Apart from that, there is increasing scientific interest in the potential role of diet (15, 16). High salt intake is an established risk factor for kidney function decline (17, 18), mainly through its adverse effect on blood pressure and vascular health (19-21). Less is known about other dietary factors. Therefore, we reviewed the current evidence on foods, beverages, and overall dietary quality in relation to the risk of incident CKD using data from prospective cohort studies.

Methods

We performed a comprehensive search in PubMed of papers published until August 2019 describing prospective cohort studies, supplemented by manual searches of reference lists from appropriate studies. The review is based on prospective cohort studies with at least three years of follow-up that reported on the relation between food groups, beverages, and dietary patterns and kidney function in populations free from CKD (defined as mean estimated glomerular filtration rate (eGFR) > 60 mL/min per 1.73 m^2).

Foods of interest were red (processed) meat, poultry, fish, dairy, vegetables, legumes, nuts, and fruits. Beverages included coffee, tea, sugar-sweetened beverages (SSBs), and diet beverages. Dietary patterns included adherence to the Dietary Approaches to Stop Hypertension (DASH) diet, Mediterranean diet, and other healthy dietary patterns. Unhealthy diets were high fat, high sugar diets, and diets with a high acid load.

Concerning kidney function, we selected studies with data on the eGFR, derived from the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (22, 23) and Modification of Diet in Renal Disease (MDRD) (24). Reasons for exclusion of articles were studies with (1) follow-up less than three years, (2) study design other than prospective cohort study, (3) study population with T2DM and analgesic use, (4) no full-text available, and (5) focus on end stage renal disease. The selection process is shown in **Supplemental Fig. 1**.

From selected papers, we extracted data on population characteristics, study design, intakes of foods and/or beverages, kidney function outcomes, risk estimates for diet-kidney function associations, and potential confounders.

The primary outcome for this review was "incident CKD" based on eGFR cut-off criteria, described in **Supplemental Table 1**. Associations between foods, beverages, and incident CKD in different studies were expressed as odds ratios (OR), obtained from logistic regression analysis, or hazard ratios (HR), obtained from Cox proportional hazard analysis with corresponding 95% confidence intervals (CI). In this review, OR and HR are both denoted as relative risks (RRs). Continuous associations between food groups, beverages, and change in eGFR are expressed as beta regression coefficients, obtained from multivariable linear regression.

RRs and betas from fully adjusted models are reported in tables with potential confounders. When these models included possible intermediates (i.e., factors could play a role in the biological pathway), risk estimates from less adjusted models are given. Two-sided P values < 0.05 for risk estimates were considered statistically significant.

Results

An overview of studies of foods, beverages, and dietary patterns and their associations with incident CKD is presented in **Supplemental Table 1**. Studies that focused on eGFR change, albuminuria, or hyperuricemia are described in **Supplemental Table 2 and 3**. Graphical displays of the point estimates with 95% CI related to incident CKD using forest plots are presented in **Figs. 1, 2, and 3**.

Foods

Meat

Two studies evaluated the consumption of red (processed) meat and poultry in relation to incident CKD (**Fig. 1**) (25, 26). Red meat intake in these studies varied between 0.17 to 0.34 servings per day (low intake) and 1.15 to 2.52 servings per day (high intake). In the Atherosclerosis Risk in Communities (ARIC) study of ~12,000 US participants with 23 years of follow-up, a total of 2632 participants developed CKD (25). In this population, the HR for high vs low intake of red meat and CKD risk was 1.19 (95% CI, 1.03; 1.36; **Fig. 1**) (25). In a study of 4881 Iranian participants followed for three years, 613 participants developed CKD with an OR of 1.73 (95% CI, 1.33; 2.24) for high vs low red meat intake (**Fig. 1**) (26). Findings for processed meat were similar to those for red meat in both studies, and no significant associations with kidney function were found for poultry (**Fig. 1**) (25).

Fish

Two studies evaluated the association between fish consumption and incident CKD (**Fig. 1**) (25, 27). The Strong Heart Study among American Indians followed 2261 participants for 5.4 years of whom 4% developed CKD. Fish intake was analysed in four categories ranging from 0 to > 15 g per day (27). No significant associations were found with an OR of 1.46 (95% CI, 0.65; 3.26) for high vs zero fish intake (27). In the ARIC study (25), fish intake was analysed in quintiles ranging from 0.07 to 0.64 servings per day. A borderline significant HR of 0.89 (95% CI, 0.78; 1.01) was found in the upper vs lower quintile of intake (**Fig. 1**) (25).

Dairy

Dairy consumption and incident CKD were examined in the ARIC study among US individuals (**Fig. 1**) (25). Intake of low-fat dairy ranged from 0.00 to 2.04 servings per day and intake of high-fat dairy from 0.13 to 1.61 servings per day (25). A significantly lower risk of CKD was found for low-fat dairy intake, with a HR of 0.75 (95% CI, 0.65; 0.85) for high vs low intake. High-fat dairy intake was also inversely associated with CKD, albeit non-significant (**Fig. 1**) (25).

Vegetables

We found three studies of vegetable intake and CKD risk (**Fig. 1**) (28-30). In a study of 1780 Iranians from the Tehran Lipid Glucose Study (TLGS), followed for six years, 319 participants developed CKD (28). Allium vegetable intake was analysed in tertiles ranging from 1 to 39 g per week (28). A significant inverse association with CKD risk was found, with a HR of 0.68 (95% CI, 0.48; 0.98) in the upper vs lower tertiles of intake (28). In 9229 participants from the Korean Genome and Epidemiology Study, 1741 incident CKD cases were reported during 8.2 years (29). Intake of non-fermented vegetables ranged from 49 to 222 g per day, and intake of fermented vegetables from 164 to 227 g per day (29). Non-fermented vegetables were inversely related to CKD risk, with a HR of 0.86 (95% CI, 0.76; 0.98) for high vs low intake (**Fig 1**) (29). For fermented vegetables, an inverse but non-significant association was found (**Fig. 1**) (29). In the abovementioned TLGS, nitrate-containing vegetable intake ranged from 146 to 428 g per day (30). No significant association with CKD risk was found after three years of follow-up (**Fig. 1**) (30).

Legumes and nuts

In the ARIC study with 23 years of follow-up, legume intake ranged from 0.07 to 0.68 servings per day and nut intake ranged from 0.03 to 0.86 servings per day (25). Both legumes and nuts were significantly associated with lower risks of CKD, with HRs of 0.83 (95% CI, 0.72; 0.95) and 0.81 (95% CI, 0.72; 0.92) for high vs low intakes, respectively (**Fig. 1**) (25).

Fruits

One study in 9229 South Koreans, followed for 8.2 years, reported on fruit consumption and incident CKD (29). Fruit intake ranged from 143 to 345 g per day and showed no association with incident CKD (HR of 1.00) (**Fig. 1**) (29).

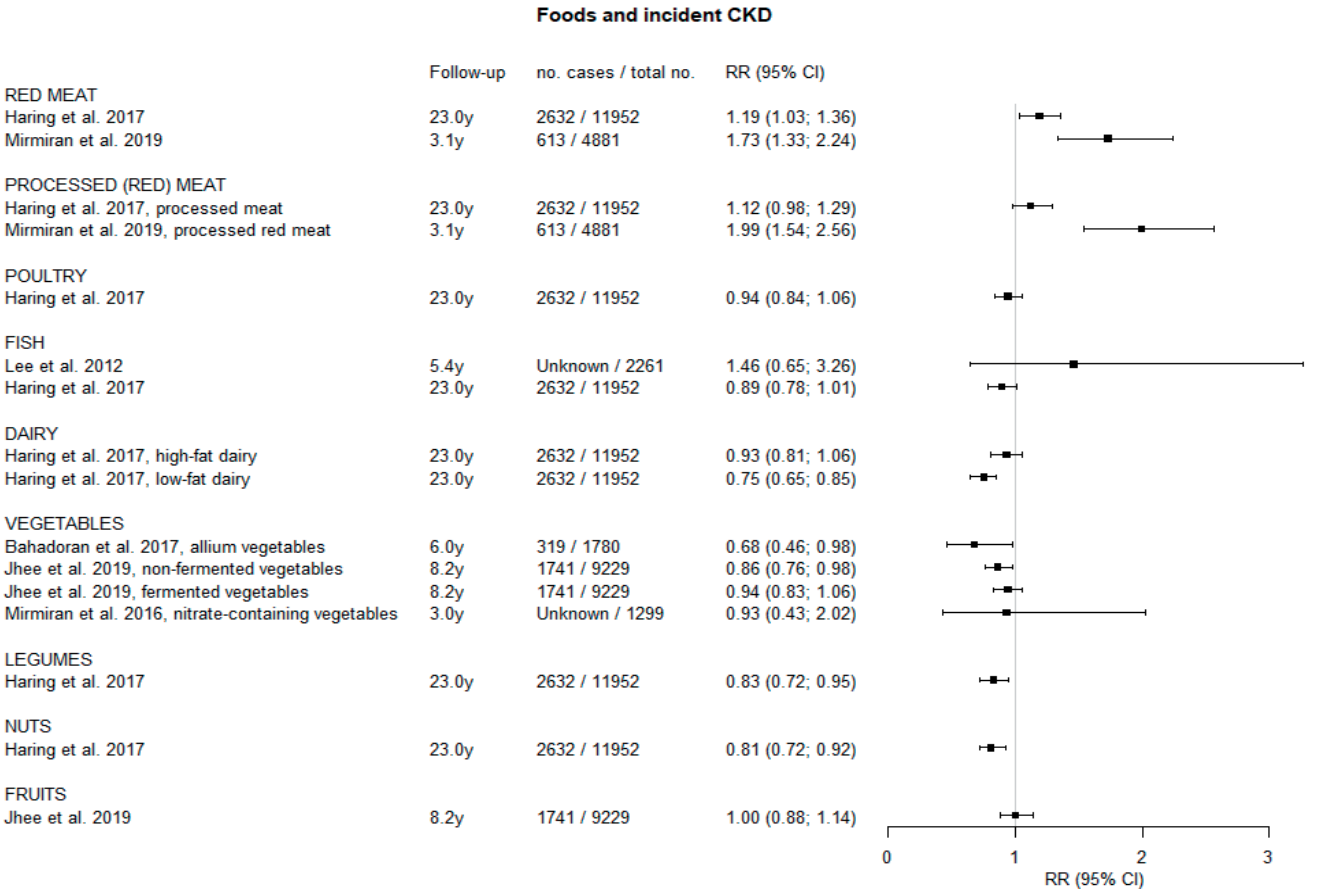

Fig. 1 Forest plot for associations between commonly consumed foods and incident chronic kidney disease.

Beverages

Coffee

Three studies examined coffee consumption and incident CKD (**Fig. 2**) (31-33). The Iranian TLGS compared coffee drinkers (median intake 8.3 mL per day) to non-drinkers (31). In the ARIC study in the USA (32) and the Korean Genome and Epidemiology Study in South Korea (33), those drinking at least three cups (32) or at least two cups (33) were compared with non-coffee drinkers. In the Iranian study, a non-significant direct association between coffee and CKD was found (31), whereas in the US and Korean studies, significant inverse associations were observed in those with higher coffee intakes, with HR of 0.84 (32) and 0.80 (33), respectively (**Fig. 2**).

Tea

The Iranian TLGS also reported on tea consumption, ranging from < 250 mL (low intake) to > 750 mL per day (high intake) (**Fig. 2**) (31). Unfortunately, data on the type of tea and its preparation method was not collected (31). However, a previous study reported that in Iran, black tea is often consumed (34) with added sweets and sugar, including a variety of additives (31). No significant association with incident CKD was found (**Fig. 2**) (31).

Soft drinks

Three studies reported on SSBs and incident CKD (**Fig. 2**) (35-37), of which one American study also reported on diet beverages (**Fig. 2**) (36). In the ARIC study with nine years of follow-up, consumption of SSBs (cut-off one drink per day) was not significantly associated with CKD risk (35). In the Jackson Heart Study (3003 participants, 185 CKD cases) with eight years of follow-up, a direct, non-significant association of SSBs with CKD risk was found (36). In the Iranian TLGS, SSB consumption ranged from <0.5 to >4 servings per week (37). A significantly elevated risk of CKD was found when comparing high with low intakes, with an OR (95% CI) of 1.92 (1.05; 3.48) (**Fig. 2**) (37). Diet beverages were studied in the Jackson Heart Study and showed no significant association with CKD risk (**Fig. 2**) (36).

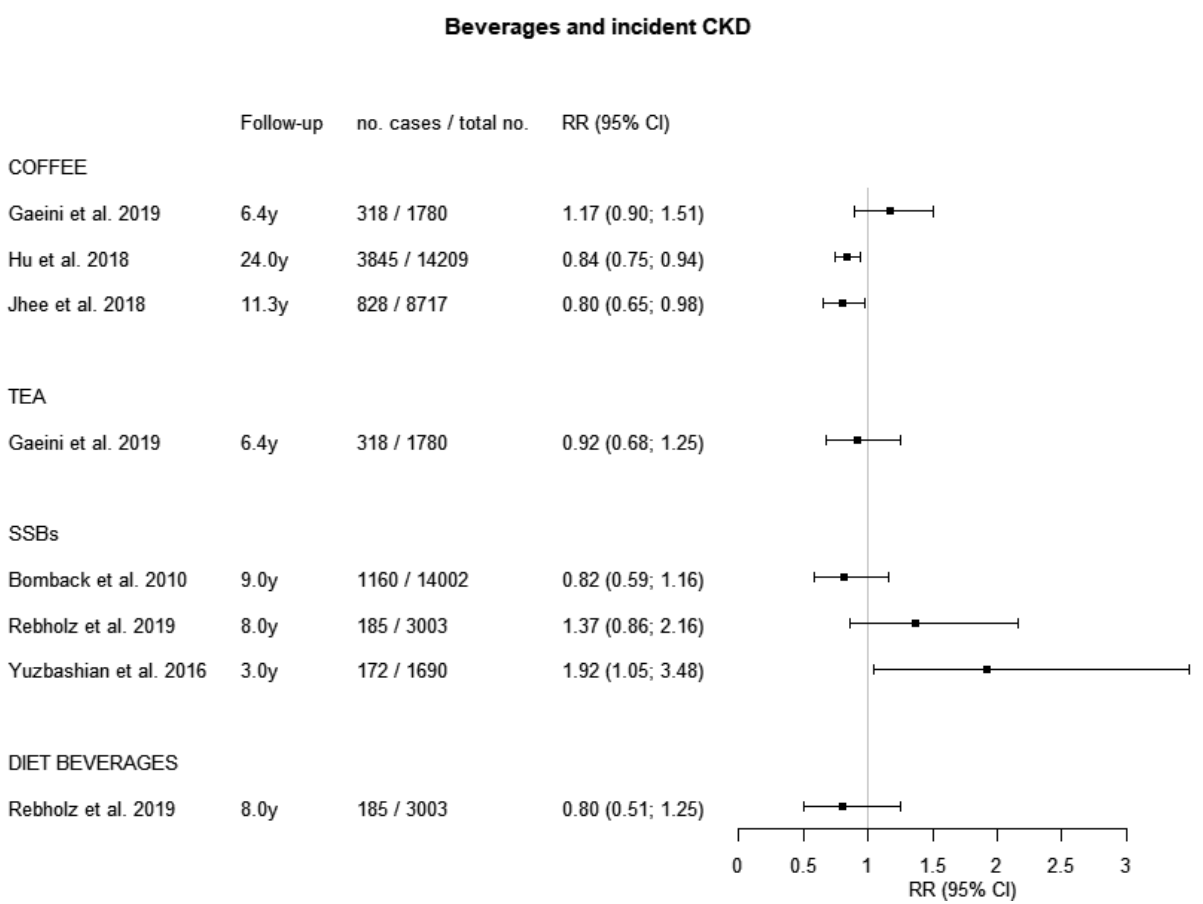

Fig. 2 Forest plot for associations between commonly consumed beverages and incident chronic kidney disease. SSBs, sugar-sweetened beverages.

Dietary patterns

Healthy diets

A number of studies examined healthy dietary patterns and incident CKD (38-44), including the DASH diet (39-41), Mediterranean diet (38, 42), and other healthy dietary patterns (42-44), for which findings are shown in **Fig. 3**. The DASH diet was examined in the Healthy Aging in Neighborhoods of Diversity across the Life Span cohort with five years of follow-up (40), in the ARIC study with 23 years of follow-up (41) and in the Iranian TLGS with 6.1 years of follow-up (39). All studies suggested a beneficial effect of the DASH diet, with RRs between 0.41 and 0.86 for high vs low adherence (**Fig. 3**). The association was statistically significant for two studies (39, 41).

Mediterranean diet scores were examined in the Northern Manhattan Study (38) and ARIC study (42), with 6.9 years (38) and 24 years (42) of follow-up, respectively. Reduced RRs of 0.50 (38) and 0.89 (42) were found for high vs low adherence, which were significant for both studies (**Fig. 3**). The ARIC study also examined (42) adherence to healthy dietary patterns assessed using the Healthy Eating Index-2015 (HEI-2015) and the alternative HEI-2010 (42). The HEI-2015 was designed to assess adherence to US Dietary Guidelines for Americans (45), while the alternative HEI-2010 was designed to identify key components associated with chronic diseases (46). For both diet quality scores, significantly lower risks of CKD were found for higher adherence, with RRs of 0.86 and 0.81, respectively (**Fig. 3**) (42).

In the ARIC study with 22 years of follow-up, the Healthy Diet Score based on American Heart Association's Life's Simple 7 was studied, which appeared not to be associated with incident CKD (43). In the Framingham Offspring cohort followed for 6.6 years (1802 participants, 171 CKD cases), the Dietary Guidelines Adherence Index was borderline significantly inversely associated with CKD risk (44).

Healthy dietary patterns were also beneficially associated with other renal function outcomes, such as rapid eGFR decline (40, 44) and ≥ 25% eGFR decline (40) (**Supplemental Table 1**).

Unhealthy diets

Two studies reported on unhealthy dietary patterns and incident CKD (**Fig. 3**) (47, 48). In the TLGS, a high-fat, high-sugar diet was related to a significantly higher risk of CKD, with OR of 1.46 (47). In participants of the ARIC study, an increased HR of 1.13 was found for a diet with a high acid load (12.2 to 100.7 mEq per day), which is characterised by high levels of salt, animal protein, and phosphorus, compared with a low acid load (− 119.1 to − 3.2 mEq per day).

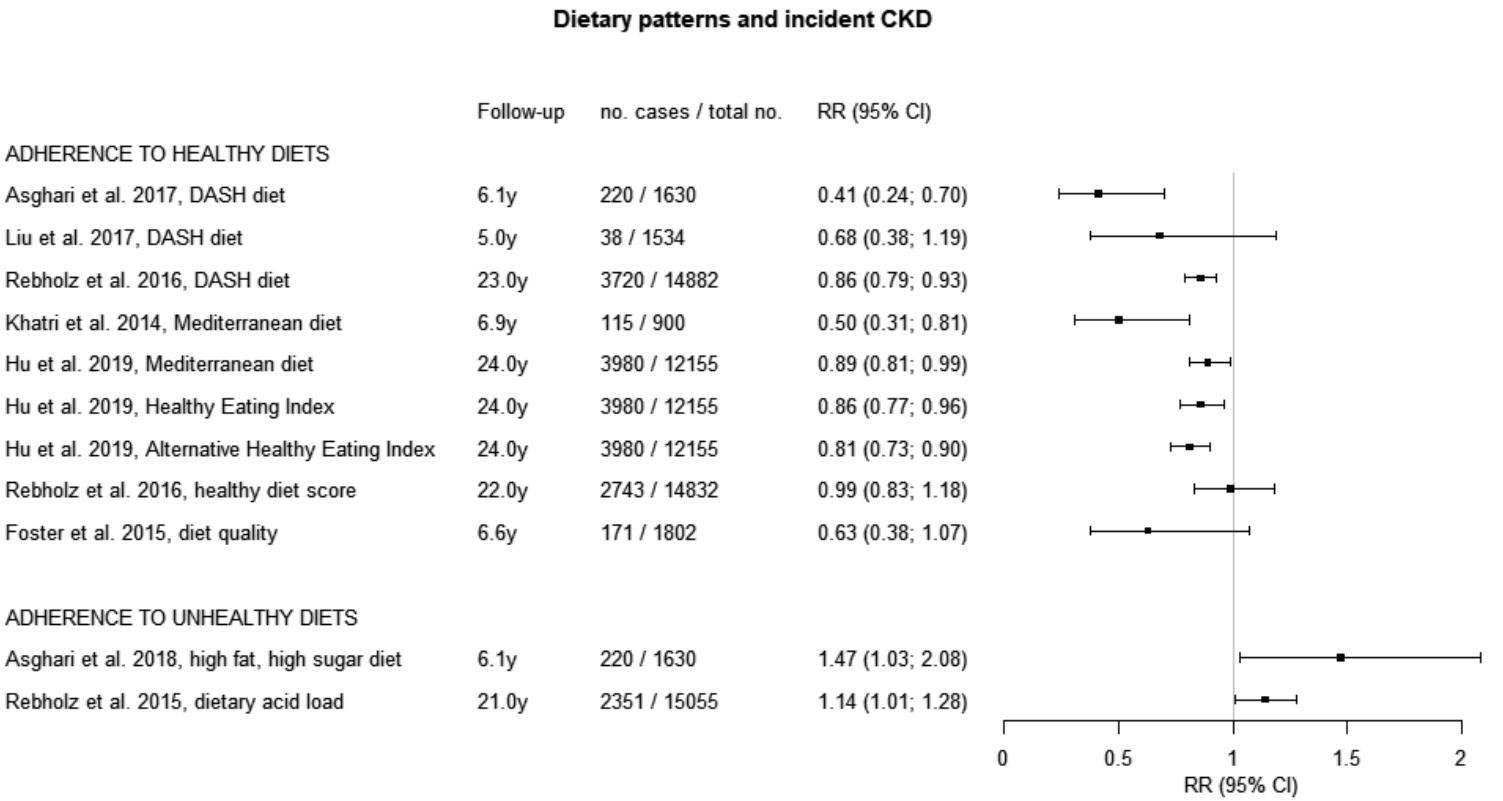

Fig. 3 Forest plot for associations between dietary patterns and incident chronic kidney disease. DASH, Dietary Approaches to Stop Hypertension.

Conclusion

This review of 21 prospective cohort studies among individuals with (relatively) normal kidney function shows a consistently lower risk of CKD in those adhering to a healthy dietary pattern (38-44). For individual food groups and beverages, the observed associations were more variable and weaker. We found adverse associations for red (processed) meat and SSBs in some studies and beneficial associations for dairy, vegetables, legumes, and nuts.

Two recent reviews have indicated that healthy dietary patterns may prevent incident CKD (15, 16). Ajjarapu et al. included 26 prospective cohort studies and found that adherence to a DASH or Mediterranean diet may be useful to prevent CKD (16). Similar results were found in a meta-analysis of 15 prospective and retrospective cohort studies performed by Bach et al. (15). A low animal/vegetable protein ratio is often considered an indicator of a healthy dietary pattern. In this regard, the ARIC study (25) showed that after 23 years of follow-up, high (> 22.8 g per day) vs low (< 12.1 g per day) intake of vegetable protein was significantly associated with lower risk of CKD, whereas no association was found for high (> 69.6 g per day) vs low (< 36.4 g per day) intake of animal protein (25). Similar results on animal protein intake were found in 1135 participants with normal renal function (defined as eGFR > 80 mL/min per 1.73 m^2) from the Nurses' Health Study (49).

A lower risk of incident CKD for those consuming more vegetables and legumes may partly be attributable to fibre, as shown in a study among Iranian TLGS participants, with 6.1 years of follow-up (50). Consumption of whole grains has also been linked to less kidney function decline in the Doetinchem Cohort Study in the Netherlands, with 15 years of follow-up (51). In a study of vegetables and fruit intake in relation to kidney function decline, assessed by the annual change in eGFR, inverse associations were found (51) (**Supplemental Table 2**), which strengthens our findings on healthy dietary patterns.

We found no association of CKD with fish intake, which is often considered part of a healthy diet. This was confirmed in another study among American Indians with 5.4 years of follow-up, where fish intake was not related to change in kidney function (27) (**Supplemental Table 2**). For poultry, we could only include one study, and more research is needed.

Our results for coffee, indicating a potentially protective effect, are also in line with the results from a study on kidney function change (52) (**Supplemental Table 2**). In this study, the coffee was mainly caffeinated (52) and likely to be filtered. The Iranian study suggested an increased, albeit non-significant, risk of CKD, which could be attributable to the regularly consumed unfiltered type of coffee in this country (31). However, more information regarding the type of coffee and its preparation methods is needed, including amounts of added sugar and other condiments, before results can be correctly interpreted. We found no beneficial

associations for tea and incident CKD, which was in line with the results from a Dutch study on kidney function decline (52) (**Supplemental Table 2**). However, our review included only one study on incident CKD from Iran (31). More information about the types of tea in relation to kidney function, including amounts of added sugar, is needed before drawing conclusions.

For low-fat dairy products and incident CKD, we found some evidence for a potentially protective effect on kidney function, though based on only one study (25). This is in line with a study in Dutch participants in which less kidney function loss was found during 15 years of follow-up who consumed more milk and low-fat dairy (53) (**Supplemental Table 2**).

With regard to other kidney function outcomes (**Supplemental Table 3**), studies on the risk of albuminuria (27, 35, 54, 55) and hyperuricemia (35) were in accordance with those for CKD. A higher, albeit non-significant risk of hyperuricemia was found for high vs low SSB consumption (35). Also, a good versus poor diet quality, based on eight fundamental DASH diet components, was associated with a lower risk of incident microalbuminuria (55), and fruit intake was related to a lower risk of albuminuria (54). Fish intake was not associated with albuminuria (27, 56).

To summarise, this review shows that a healthy dietary pattern may help prevent kidney function decline and lower the risk of CKD. The number of studies of individual foods and beverages in this field, however, is limited and most of the evidence comes from a limited number of cohorts. More research on the components of healthy (and unhealthy) diets and indicators of kidney health in different populations is needed to fill these knowledge gaps.

Compliance with ethical standards

Conflict of Interest The research presented in this paper has been funded by the Jaap Schouten Foundation (JSF_SU_10_2018).

Human and Animal Rights and Informed Consent All reported studies/experiments with human subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki Declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

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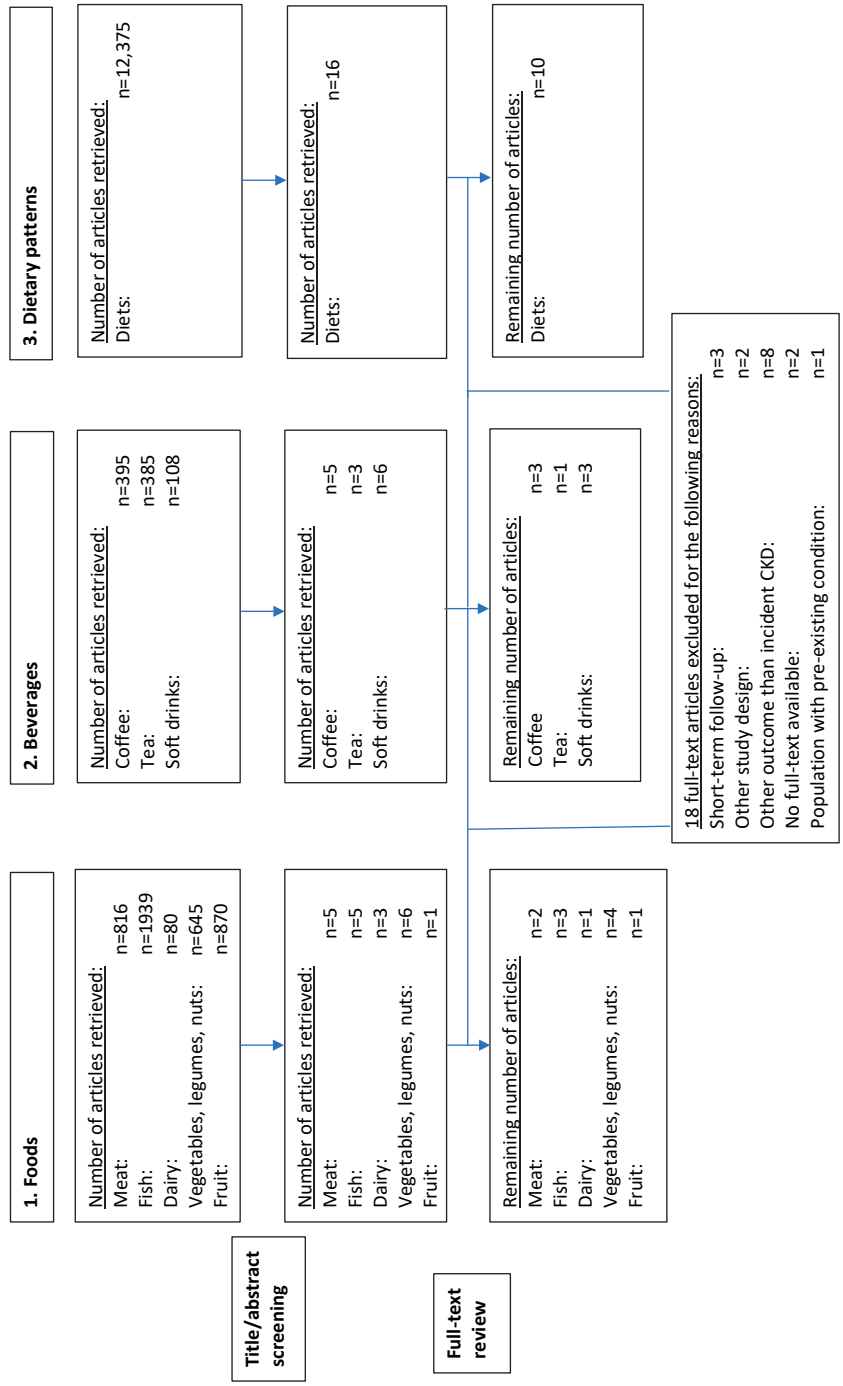

Supplemental Fig. 1 Flowchart of the literature search on diet and kidney function.

Supplemental Table 1 Overview of prospective population-based studies of food and beverage intake and risk of chronic kidney diseases.

Food, beverage or dietary pattern	Author, year	Study population, country	Baseline characteristics	No. cases / total no.	
Red meat	Haring *et al.* 2017	Community-based ARIC study, USA	●Women: 56% ●Age: 54 ± 6y ●Black race: 23% ●eGFR: 103 ± 14 mL/ min per 1.73 m^2 ●Animal protein intake: 46 ± 8 g/day	2632 / 11,952	
Red meat	Mirmiran *et al.* 2019	Community-based TLGS, Iran	●Men: 54% ●Age: 40 ± 13y ●eGFR: 76 ± 0.2 mL/ min per 1.73 m^2 ●Red meat intake: 1 serving/day	613 / 4881	
Processed meat	Haring *et al.* 2017	Community-based ARIC study, USA	●Women: 56% ●Age: 54 ± 6y ●Black race: 23% ●eGFR: 103 ± 14 mL/ min per 1.73m^2 ●Animal protein intake: 46 ± 8 g/day	2632 / 11,952	
Processed red meat	Mirmiran *et al.* 2019	Community-based TLGS, Iran	●Men: 54% ●Age: 40 ± 13y ●eGFR: 76 ± 0.2 mL/ min per 1.73 m^2 ●Red meat intake: 1 serving/day	613 / 4881	

	Follow-up period	Dietary assessment	Outcome definition + ascertainment	Fully adjusted point estimate (95% CI)[a]	Confounders
	Median: 23.0y	Validated 66-item FFQ	●Incident CKD, defined as meeting one of the following criteria: 1)eGFR decrease ≥25% from baseline resulting in eGFR <60 mL/min per 1.73 m^2 2)CKD-related hospitalisation 3)CKD-related death or 4)ESRDs ●eGFR calculated with 2009 CKD-EPI equation$_{creatinine}$	Q5 vs Q1 HR (95% CI) = 1.19 (1.03; 1.36)*	● age, sex, race-center ● BMI, WHR ● current smoker ● alcohol intake ● PA index, leisure-related PA ● education level ● total caloric intake ● total carbohydrate intake ● HDL-c, LDL-c, TGs, total cholesterol ● SBP ● lipid-lowering medication use, anti-hypertensive medication use
	Median: 3.1y	Validated 168-item FFQ	●Incident CKD, defined as eGFR<60 mL/min per 1.73 m^2 ●eGFR assessed with MDRD equation	Q4 vs Q1 OR (95% CI) = 1.73 (1.33; 2.24)*	● age, sex ● BMI ● smoking ● PA ● total energy intake ● prevalent diabetes ● TGs ● hypertension
	Median: 23.0y	Validated 66-item FFQ	●Incident CKD, defined as meeting one of the following criteria: 1)eGFR decrease ≥25% from baseline resulting in eGFR <60 mL/min per 1.73 m^2 2)CKD-related hospitalisation 3)CKD-related death or 4)ESRDs ●eGFR calculated with 2009 CKD-EPI equation$_{creatinine}$	Q5 vs Q1 HR (95% CI) = 1.12 (0.98; 1.29)	● age, sex, race-center ● BMI, WHR ● current smoker ● alcohol intake ● PA index, leisure-related PA ● education level ● total caloric intake ● total carbohydrate intake ● HDL-c, LDL-c, TGs, total cholesterol ● SBP ● lipid-lowering medication use, anti-hypertensive medication use
	Median: 3.1y	Validated 168-item FFQ	●Incident CKD, defined as eGFR<60 mL/min per 1.73 m^2 ●eGFR assessed with MDRD equation	Q4 vs Q1 OR (95% CI) = 1.99 (1.54; 2.56)*	● age, sex ● BMI ● smoking ● PA ● total energy intake ● prevalent diabetes ● TGs ● hypertension

Supplemental Table 1 continued

Food, beverage or dietary pattern	Author, year	Study population, country	Baseline characteristics	No. cases / total no.	
Poultry	Haring *et al.* 2017	Community-based ARIC study, USA	●Women: 56% ●Age: 54 ± 6y ●Black race: 23% ●eGFR: 103 ± 14 mL/ min per 1.73 m^2 ●Animal protein intake: 46 ± 8 g/day	2632 / 11,952	
Fish	Lee *et al.* 2012	Strong Heart Study in American Indians, USA	●Men: 38% ●Age: 38 ± 16y ●eGFR: 102 ± 26 mL/ min per 1.73 m^2 ●Fish intake 0 g/day: 18% >15.0 g/day: 13% ≤15 g/day: 69%	Unknown / 2261	
Fish and seafood	Haring *et al.* 2017	Community-based ARIC study, USA	●Women: 56% ●Age: 54 ± 6y ●Black race: 23% ●eGFR: 103 ± 14 mL/ min per 1.73 m^2 ●Animal protein intake: 46 ± 8 g/day	2632 / 11,952	
Low-fat and high-fat dairy	Haring *et al.* 2017	Community-based ARIC study, USA	●Women: 56% ●Age: 54 ± 6y ●Black race: 23% ●eGFR: 103 ± 14 mL/ min per 1.73 m^2 ●Animal protein intake: 46 ± 8 g/day	2632 / 11,952	

	Follow-up period	Dietary assessment	Outcome definition + ascertainment	Fully adjusted point estimate (95% CI)[a]	Confounders
	Median: 23.0y	Validated 66-item FFQ	●Incident CKD, defined as meeting one of the following criteria: 1)eGFR decrease ≥25% from baseline resulting in eGFR <60 mL/min per 1.73 m^2 2)CKD-related hospitalisation 3)CKD-related death or 4)ESRDs ●eGFR calculated with 2009 CKD-EPI equation$_{creatinine}$	Q5 vs Q1 HR (95% CI) = 0.94 (0.84; 1.06)	● age, sex, race-center ● BMI, WHR ● current smoker ● alcohol intake ● PA index, leisure-related PA ● education level ● total caloric intake ● total carbohydrate intake ● HDL-c, LDL-c, TGs, total cholesterol ● SBP ● lipid-lowering medication use, anti-hypertensive medication use
	Mean: 5.4y	119-item Block FFQ	●Incident CKD, defined as eGFR<60 mL/min per 1.73 m^2 ●eGFR assessed with MDRD equation	>15 g/day vs 0 g/day OR (95% CI) = 1.46 (0.65; 3.26)	● age, sex, center ● WHR ● smoking ● total energy intake ● protein intake, sodium intake ● prevalent diabetes ● TGs ● SBP ● urinary ACR
	Median: 23.0y	Validated 66-item FFQ	●Incident CKD, defined as meeting one of the following criteria: 1)eGFR decrease ≥25% from baseline resulting in eGFR <60 mL/min per 1.73 m^2 2)CKD-related hospitalisation 3)CKD-related death or 4)ESRDs ●eGFR calculated with 2009 CKD-EPI equation$_{creatinine}$	Q5 vs Q1 HR (95% CI) = 0.89 (0.78; 1.01)	● age, sex, race-center ● BMI, WHR ● current smoker ● alcohol intake ● PA index, leisure-related PA ● education level ● total caloric intake ● total carbohydrate intake ● HDL-c, LDL-c, TGs, total cholesterol ● SBP ● lipid-lowering medication use, anti-hypertensive medication use
	Median: 23.0y	Validated 66-item FFQ	●Incident CKD, defined as meeting one of the following criteria: 1)eGFR decrease ≥25% from baseline resulting in eGFR <60 mL/min per 1.73 m^2 2)CKD-related hospitalisation 3)CKD-related death or 4)ESRDs ●eGFR calculated with 2009 CKD-EPI equation$_{creatinine}$	**Low-fat dairy** Q5 vs Q1 HR (95% CI) = 0.75 (0.65; 0.85)* **High-fat dairy** Q5 vs Q1 HR (95% CI) = 0.93 (0.81; 1.06)	● age, sex, race-center ● BMI, WHR ● current smoker ● alcohol intake ● PA index, leisure-related PA ● education level ● total caloric intake ● total carbohydrate intake ● HDL-c, LDL-c, TGs, total cholesterol ● SBP ● lipid-lowering medication use, anti-hypertensive medication use

Supplemental Table 1 continued

Food, beverage or dietary pattern	Author, year	Study population, country	Baseline characteristics	No. cases / total no.	
Allium vegetables	Bahadoran *et al.* 2017	Community-based TLGS, Iran	●Men: 44% ●Age: 40 ± 14y ●eGFR: 78 ± 0.3 mL/min per 1.73 m^2 ●Allium vegetables intake: 17 g/week	319 / 1780	
Vegetables	Jhee *et al.* 2019	Community-based KoGES, South Korea	●Men: 48% ●Age: 52 ± 9y ●eGFR: 94 ± 14 mL/min per 1.73m^2 ●Non-fermented vegetable intake: 129 ± 127 g/day ●Fermented vegetable intake: 203 ± 145 g/day	1741 / 9229	
NCVs	Mirmiran *et al.* 2016	Community-based TLGS, Iran	●Men: 43% ●Age: 38 ± 12y ●eGFR: 80 ± 1 mL/min per 1.73 m^2 ●NCVs intake: 298 ± 177 g/day	Unknown / 1299	
Legumes	Haring *et al.* 2017	Community-based ARIC study, USA	●Women: 56% ●Age: 54 ± 6y ●Black race: 23% ●eGFR: 103 ± 14 mL/min per 1.73 m^2 ●Animal protein intake: 46 ± 8 g/day	2632 / 11,952	

	Follow-up period	Dietary assessment	Outcome definition + ascertainment	Fully adjusted point estimate (95% CI)[a]	Confounders
	Mean: 6.0y	Validated 168-item semiquantitative FFQ	●Incident CKD defined as eGFR<60 mL/min per 1.73 m^2 ●eGFR assessed with $CKD\text{-}EPI_{creatinine}$ equation	T3 vs T1 HR (95% CI) = 0.68 (0.46; 0.98)*	● age, sex ● BMI ● smoking ● PA ● dietary pattern scores ● T2D ● TGs to HDL-c ratio
	Mean: 8.2y	Validated 106-item semiquantitative FFQ	●Incident CKD defined as eGFR<60 mL/min per 1.73 m^2 ● eGFR assessed with $CKD\text{-}EPI_{creatinine}$ equation	**Nonfermented vegetables** T3 vs T1 HR (95% CI) = 0.86 (0.76; 0.98)* **Fermented vegetables** T3 vs T1 HR (95% CI) = 0.94 (0.83; 1.06)	● age, sex ● BMI ● smoking status ● alcohol status ● PA ● education level ● total energy intake ● red or nonred meat, fish, dairy, egg, legume, nut, grain intake ● history of hypertension and diabetes ● LDL-c ● SBP ● serum albumin, hemoglobin ● eGFR, proteinuria level
	Mean: 3.0y	Validated 168-item semiquantitative FFQ	●Incident CKD, defined as eGFR<60 mL/min per 1.73 m^2 ●eGFR assessed with $CKD\text{-}EPI_{creatinine}$ equation	T3 vs T1 OR (95% CI) = 0.93 (0.43; 2.02)	● age, sex ● BMI ● smoking ● PA ● education ● dietary intake of energy ● fiber, potassium intake ● diabetes ● hypertension
	Median: 23.0y	Validated 66-item FFQ	●Incident CKD, defined as meeting one of the following criteria: 1)eGFR decrease ≥25% from baseline resulting in eGFR <60 mL/min per 1.73 m^2 2)CKD-related hospitalisation 3)CKD-related death or 4)ESRDs ●eGFR calculated with 2009 CKD-EPI $equation_{creatinine}$	Q5 vs Q1 HR (95% CI) = 0.83 (0.72; 0.95)*	● age, sex, race-center ● BMI, WHR ● current smoker ● alcohol intake ● PA index, leisure-related PA ● education level ● total caloric intake ● total carbohydrate intake ● HDL-c, LDL-c, TGs, total cholesterol ● SBP ● lipid-lowering medication use, anti-hypertensive medication use

Supplemental Table 1 continued

Food, beverage or dietary pattern	Author, year	Study population, country	Baseline characteristics	No. cases / total no.	
Nuts	Haring *et al.* 2017	Community-based ARIC study, USA	●Women: 56% ●Age: 54 ± 6y ●Black race: 23% ●eGFR: 103 ± 14 mL/min per 1.73 m^2 ●Animal protein intake: 46 ± 8 g/day	2632 / 11,952	
Fruit	Jhee *et al.* 2019	Community-based KoGES, South Korea	●Men: 48% ●Age: 52 ± 9y ●eGFR: 94 ± 14 mL/min per 1.73 m^2 ●fruit intake: 269 ± 332 g/day	1741 / 9229	
Coffee	Gaeini *et al.* 2019	Community-based TLGS, Iran	●Men: 41% ●Age: 34 ± 15y ●eGFR: 79 ± 12 mL/min per 1.73 m^2 ●Coffee intake: 14 ± 55 mL/day	318 / 1780	
Coffee	Hu *et al.* 2018	Community-based ARIC Study, USA	●Women: 56% ●Age: 54 ± 6y ●White race: 75% ●Black race: 25% ●eGFR: 103 ± 14 mL/min per 1.73 m^2 ●Coffee intake Never: 19% <1 cup/d: 21% ≥1-<2 cups/d: 25% ≥2-<3 cups/d: 15% ≥3 cups/d:19%	3845 / 14,209	

	Follow-up period	Dietary assessment	Outcome definition + ascertainment	Fully adjusted point estimate (95% CI)[a]	Confounders
	Median: 23.0y	Validated 66-item FFQ	●Incident CKD, defined as meeting one of the following criteria: 1)eGFR decrease ≥25% from baseline resulting in eGFR <60 mL/min per 1.73 m^2 2)CKD-related hospitalisation 3)CKD-related death or 4)ESRDs ●eGFR calculated with 2009 CKD-EPI equation$_{creatinine}$	Q5 vs Q1 HR (95% CI) = 0.81 (0.72; 0.92)*	● age, sex, race-center ● BMI, WHR ● current smoker ● alcohol intake ● PA index, leisure-related PA ● education level ● total caloric intake ● total carbohydrate intake ● HDL-c, LDL-c, TGs, total cholesterol ● SBP ● lipid-lowering medication use, anti-hypertensive medication use
	Mean: 8.2y	Validated 106-item semiquantitative FFQ	●Incident CKD defined as eGFR <60 mL/min per 1.73 m^2 ●eGFR assessed with CKD-EPI$_{creatinine}$	T3 vs T1 HR (95% CI) = 1.00 (0.88; 1.14)	● age, sex ● BMI ● smoking status ● alcohol status ● PA ● education level ● total energy intake ● red or nonred meat, fish, dairy, egg, legume, nut, grain intake ● history of hypertension and diabetes ● LDL-c ● SBP ● serum albumin, hemoglobin ● eGFR, proteinuria level
	Mean: 6.4y	Validated 168-item FFQ	●Incident CKD, defined as eGFR <60 mL/min per 1.73 m^2 ●eGFR assessed with CKD-EPI$_{creatinine}$ equation	Drinker vs non-drinker: HR (95% CI) = 1.17 (0.90; 1.51)	● age, sex ● BMI ● smoking ● total energy ● fiber, tea ● dietary fat ● TGs to HDL-c ratio
	Median: 24.0y	66-item semi-quantitative FFQ	●Incident CKD defined as meeting at least one of following criteria: 1)eGFR<60mL/min per 1.73 m^2 2)ICD-9/10 code for CKD stage ≥3 related hospitalisation 3)ICD-9/10 code for death related to CKD stage ≥3 4)ESRD ●eGFR assessed with CKD-EPI$_{creatinine}$ equation	≥3 cups/d vs non-coffee drinker HR (95% CI) = 0.84 (0.75; 0.94)*	● age, sex, race-center ● BMI ● smoking ● alcohol status ● PA ● education ● total energy intake ● DASH diet score ● diabetes status ● SBP ● anti-hypertensive medication use ● baseline eGFR

Supplemental Table 1 continued

Food, beverage or dietary pattern	Author, year	Study population, country	Baseline characteristics	No. cases / total no.	
Coffee	Jhee *et al.* 2018	Community-based KoGES, South Korea	●Men: 48% ●Age: 52 ± 9y ●eGFR: 94 ± 14 mL/min per 1.73 m^2 ●Coffee intake Never: 23.0% <1 cup/week: 7% 1-6 cups/week: 18% 1 cup/day: 27% ≥2 cups/day: 26%	828 / 8717	
Tea	Gaeini *et al.* 2019	Community-based TLGS, Iran	●Men: 41% ●Age: 34 ± 15y ●eGFR: 79 ± 12 mL/min per 1.73 m^2 ●Tea intake: 570 ± 553 mL/day	318 / 1780	
Sugar-sweetened soda	Bomback *et al.* 2010	Community-based ARIC Study, USA	●Women: 55% ●Age: 54 ± 6y ●Race White: 73% Black: 27% Other: 0.3% ●eGFR: 92 ± 21 mL/min per 1.73 m^2 ●Soda drinking <1 soda/day: 82% 1 soda/day: 12% >1 soda/day: 6%	1160 / 14,002	
SSB	Rebholz *et al.* 2019	Community-based Jackson Heart Study, USA	●Women: 64% ●Age: 54 ± 12y ●eGFR: 98 ± 18 mL/min per 1.73 m^2	185 / 3003	

	Follow-up period	Dietary assessment	Outcome definition + ascertainment	Fully adjusted point estimate (95% CI)[a]	Confounders
	Mean: 11.3y	Validated semi-quantitative FFQ	●Incident CKD defined as eGFR<60 mL/min per 1.73 m^2 ●eGFR assessed with $CKD\text{-}EPI_{creatinine}$	≥2 cups/d vs non-coffee drinker HR (95% CI) = 0.80 (0.65; 0.98)*	● age, sex ● BMI ● smoking status ● alcohol status ● education levels, income ● daily intake amount of tea and chocolate ● history of hypertension and CVD events ● HbA1c, history of diabetes ● CRP, hemoglobin, albumin ● total cholesterol ● mean arterial pressure ● eGFR, proteinuria
	Mean: 6.4y	Validated 168-item FFQ	●Incident CKD, defined as eGFR<60 mL/min per 1.73 m^2 ●eGFR assessed with $CKD\text{-}EPI_{creatinine}$ equation	>750 mL/d vs <250 mL/d: HR (95% CI) = 0.92 (0.68; 1.25)	● age, sex ● BMI ● smoking ● total energy ● fiber, coffee ● dietary fat ● TGs to HDL-c ratio
	Mean: 9.0y	Validated 66-item semiquantitative FFQ	●Incident CKD defined as eGFR <60 mL/min per 1.73 m^2 ●eGFR assessed with MDRD equation	>1 soda/d vs <1 soda/d OR (95% CI) = 0.82 (0.59; 1.16)	● age, sex, race, ARIC-field center ● BMI ● current tobacco use ● alcohol use ● caloric intake ● sodium intake ● diabetes ● hypertension
	Median: 8.0y	Validated 158-item modified, version of Lower Mississippi Delta Nutrition Intervention Research Initiative FFQ	●Incident CKD defined as eGFR <60 mL/min per 1.73 m^2 accompanied by ≥30% eGFR decline ●eGFR assessed with $CKD\text{-}EPI_{creatinine}$ equation	T3 vs T1 OR (95% CI) = 1.37 (0.86; 2.16)	● age, sex ● BMI ● smoking status ● PA index ● education ● total energy intake ● healthy and Southern dietary pattern score ● diabetes ● history of CVD ● HDL-c, LDL-c ● hypertension ● baseline eGFR

Supplemental Table 1 continued

Food, beverage or dietary pattern	Author, year	Study population, country	Baseline characteristics	No. cases / total no.	
SSBs and SSSDs	Yuzbashian *et al.* 2016	Community-based TLGS, Iran	●Women: 54% ●Age: 45 ± 12y ●eGFR: 70 ± 15 mL/min per 1.73 m^2 ●SSB intake: 2 servings/week	172 / 1690	
Diet beverages	Rebholz *et al.* 2019	Community-based Jackson Heart Study, USA	●Women: 64% ●Age: 54 ± 12y ●eGFR: 98 ± 18 mL/min per 1.73 m^2	185 / 3003	
Adherence to DASH diet	Asghari *et al.* 2017	Community-based TLGS, Iran	●Women: 51% ●Age: 43 ± 11y ●eGFR: 73 ± 8 mL/min per 1.73 m^2 ●DASH diet score: 24	220 / 1630	
Adherence to DASH diet	Liu *et al.* 2017	Population-based HANDLS study, USA	●Men: 42% ●Age: 48 ± 9y ●African American race: 59% ●eGFR: 95 [82; 108] mL/min per 1.73 m^2 ●DASH accordance score: 2 [1; 3]	**Incident CKD** 38 / 1534 **Rapid eGFR decline** 193 / 1534 **eGFR decline ≥25% during follow-up** 65 / 1534	

	Follow-up period	Dietary assessment	Outcome definition + ascertainment	Fully adjusted point estimate (95% CI)[a]	Confounders
	Mean: 3.0y	168-item FFQ	●Incident CKD defined as eGFR <60 mL/min per 1.73 m^2 ●eGFR assessed with MDRD equation	**SSBs** >4 servings/week vs <0.5 servings/week OR (95% CI) = 1.92 (1.05; 3.48)* **SSSDs** >4 servings/week vs <0.5 servings/week OR (95% CI) = 2.04 (1.06; 3.91)*	● age, sex ● BMI ● smoking ● PA ● energy intake ● sodium ● diabetes ● hypertension
	Median: 8.0y	Validated 158-item modified, version of Lower Mississippi Delta Nutrition Intervention Research Initiative FFQ	●Incident CKD defined as eGFR <60 mL/min per 1.73 m^2 accompanied by ≥30% eGFR decline ●eGFR assessed with $CKD\text{-}EPI_{creatinine}$ equation	T3 vs T1 OR (95% CI) = 0.80 (0.51; 1.25)	● age, sex ● BMI ● smoking status ● PA index ● education ● total energy intake ● healthy and Southern dietary pattern score ● diabetes ● history of CVD ● HDL-c, LDL-c ● hypertension ● baseline eGFR
	Median: 6.1y	Validated 168-item FFQ	●Incident CKD, defined as eGFR <60 mL/min per 1.73 m^2 ●eGFR assessed with MDRD equation	Q5 vs Q1 OR (95% CI) = 0.41 (0.24; 0.70)*	● age, sex ● BMI ● smoking ● PA ● total energy intake ● diabetes ● TGs ● hypertension ● eGFR
	Median: 5.0y	24h self-reported food intake	●Incident CKD, defined as eGFR<60 mL/min per 1.73 m^2 ●Rapid eGFR decline, defined as eGFR decline >3 mL/min per 1.73 m^2 per year ●eGFR decline ≥25% from baseline onwards ●eGFR assessed with $CKD\text{-}EPI_{creatinine}$ equation	**Incident CKD** High vs low DASH accordance OR (95% CI) = 0.68 (0.38; 1.19) **Rapid eGFR decline** High vs low DASH accordance OR (95% CI) = 0.82 (0.61; 1.09) **eGFR decline ≥25%** High vs low DASH accordance OR (95% CI) = 0.77 (0.45; 1.32)	**Rapid kidney function decline** ● age, sex, race ● tobacco use ● education level, poverty status ● total energy intake ● diabetes ● hypertension, SBP **Incident CKD + eGFR decline ≥25%** ● age, sex, race ● poverty status

Supplemental Table 1 continued

Food, beverage or dietary pattern	Author, year	Study population, country	Baseline characteristics	No. cases / total no.	
Adherence to DASH diet	Rebholz *et al.* 2016	Community-based ARIC study, USA	**T1 (low DASH diet score)** ●Women: 44% ●Age: 54 ± 6y ●eGFR: 104 ± 15 mL/ min per 1.73 m^2 **T2 (moderate DASH diet score)** ●Women: 56% ●Age: 54 ± 6y ●eGFR: 103 ± 14 mL/ min per 1.73 m^2 **T3 (high DASH diet score)** ●Women: 68% ●Age: 55 ± 6y ●eGFR: 102 ± 13 mL/ min per 1.73 m^2	3720 / 14,882	
Adherence to MeDi	Khatri *et al.* 2014	Community-based NOMAS, USA	●Men: 41% ●Age: 64 ± 8y ●eGFR: 83 ± 20 mL/min per 1.73 m^2 ●Race/ethnicity White: 15% Black: 18% Hispanic: 65% Other: 3%	115 / 900	
Adherence to healthy dietary patterns measured by HEI-2015, aHEI-2010, alternate MeDi	Hu *et al.* 2019	Community-based ARIC study, USA	●Women: 69% ●Age: 54 ± 6y ●Black race: 23% ●eGFR: 103 ± 14 mL/ min per 1.73 m^2	3980 / 12,155	

	Follow-up period	Dietary assessment	Outcome definition + ascertainment	Fully adjusted point estimate (95% CI)[a]	Confounders
	Median: 23.0y	Semi-quantitative 66-item FFQ	●Incident CKD, defined as 1) eGFR <60 mL/min per 1.73 m^2 accompanied by ≥25% eGFR decline from baseline or 2) kidney disease related hospitalisation or death or 3)ESRD ●eGFR was calculated with 2009 CKD-EPI$_{creatinine}$ equation	T3 vs T1 HR (95% CI)= 0.86 (0.79; 0.93)*	● age, sex, race-center ● overweight, obesity status ● smoking status ● PA ● education level ● total caloric intake ● diabetes ● hypertension, SBP ● ACE inhibitor use, ARB use ● baseline eGFR
	Mean: 6.9y	Modified Block National Cancer Institute FFQ	●Incident CKD, defined as <60 mL/min per 1.73 m^2 ●eGFR assessed with MDRD equation	**MeDi score ≥5 vs <5** OR (95% CI) = 0.50 (0.31; 0.81)*	● age, sex, race ● BMI ● smoking status ● PA ● education, insurance status ● diabetes ● LDL-c, HDL-c ● hypertension ● ACE inhibitor or ARB usage ● baseline eGFR
	Median: 24.0y	Semiquantitative 66-item FFQ	●Incident CKD, defined as 1) eGFR <60 mL/min per 1.73 m^2 accompanied by ≥25% eGFR decline from baseline or 2) kidney disease related hospitalisation or death or 3)ESRD ●eGFR assessed with CKD-EPI$_{creatinine}$ equation	**HEI-2015** Q5 vs Q1 HR (95% CI) = 0.86 (0.77; 0.96)* **aHEI-2010** Q5 vs Q1 HR (95% CI) = 0.81 (0.73; 0.90)* **aMed** Q5 vs Q1 HR (95% CI) = 0.89 (0.81; 0.99)*	● age, sex, race-center ● BMI ● smoking status, pack-years ● PA ● education, income ● total energy intake ● dietary acid load ● diabetes ● HDL-c ● SBP ● anti-hypertensive medication use ● eGFR

Supplemental Table 1 continued

Food, beverage or dietary pattern	Author, year	Study population, country	Baseline characteristics	No. cases / total no.	
Healthy diet score	Rebholz *et al.* 2016	Community-based ARIC study, USA	●Women: 55% ●Age: 54 ± 6y ●Black race: 26% ●African-American race: 26% ●eGFR: 103 ± 14 mL/min per 1.73 m^2	2743 / 14,832	
Diet quality	Foster *et al.* 2015	Framingham Offspring Cohort, USA	●Women: 55% ●Age: 59 ± 9y ●DGAI Low: 6 ± 1 High: 13 ± 1	**Incident CKD** 171 / 1802 **Rapid eGFR decline** 238 / 1964	
High-fat, high-sugar diet	Asghari *et al.* 2018	Community-based TLGS, Iran	●Women: 51% ●Age: 43 ± 11y ●eGFR: 74 ± 9 mL/min per 1.73 m^2	220 / 1630	
Dietary acid load	Rebholz *et al.* 2015	Community-based ARIC study, USA	●Women: 55% ●Age: 54 ± 6y ●Black: 26% ●African-American: 26% ●eGFR: 103 ± 14 mL/min per 1.73 m^2 ●Renal acid load: 5 [-3; 12] mEq/day	2351 / 15,055	

[a] Fully adjusted point estimates, but without potential mediators of the association, are presented. *Indicating statistically significant estimates. HR, hazard ratio; OR, odds ratio; CI, confidence interval; ARIC, Atherosclerosis Risk in Communities; USA, United States of America; eGFR, estimated glomerular filtration Rate; FFQ, food frequency questionnaire; CKD, chronic kidney disease; ESRD, end-stage renal disease; CKD-EPI, Chronic Kidney Disease Epidemiology collaboration; PA, physical activity; HDL, high-density lipoprotein; BMI, body mass index; WHR, waist-hip ratio; TLGS, Tehran Lipid Glucose Study; MDRD, Modification in Diet and Renal Disease; ACR, albumin-to-creatinine; TGs to HDL-c ratio, triglycerides to high-density lipoprotein-cholesterol ratio; KoGES, Korean Genome and Epidemiology Study; LDL-c, low-density lipoprotein-cholesterol; NCVs, nitrate-containing vegetables; ICD, international classification of disease; DASH, Dietary Approach to Stop Hypertension; SBP, systolic blood pressure; CVD, cardiovascular disease; HbA1c, hemoglobin A1c; CRP, C-reactive protein; SSSDs, sugar-sweetened carbonated soft drinks; SSBs, sugar-sweetened beverages; HANDLS, Healthy Aging in Neighborhoods of Diversity across the Life Span; MeDi, Mediterranean diet; NOMAS, Northern Manhattan Study; ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blockers; HEI, Healthy Eating Index; aHEI, alternative Healthy Eating Index; DGAI, Dietary Guidelines Adherence Index.

	Follow-up period	Dietary assessment	Outcome definition + ascertainment	Fully adjusted point estimate (95% CI)[a]	Confounders
	Median: 22.0y	Semiquantitative 66-item FFQ	●Incident CKD, defined as 1) eGFR <60 mL/min per 1.73 m^2 accompanied by ≥25% eGFR decline from baseline or 2) kidney disease related hospitalisation or death or 3)ESRD ●eGFR was calculated with 2009 $CKD\text{-}EPI_{creatinine}$ equation	**Ideal vs poor** HR (95% CI) = 0.99 (0.83; 1.18)	● age, sex, race ● baseline eGFR
	Mean: 6.6y	Harvard semi-quantitative FFQ	●Incident CKD, defined as eGFR<60 mL/min per 1.73 m^2 ●Rapid eGFR decline, defined as eGFR decline ≥3 mL/min per 1.73 m^2 per year ●eGFR assessed with $CKD\text{-}EPI_{creatinine}$ equation	**Incident CKD** Q4 vs Q1 OR (95% CI) = 0.63 (0.38; 1.07) **Rapid eGFR decline** Q4 vs Q1 OR (95% CI) = 0.69 (0.45; 1.05)	● age, sex ● BMI ● diabetes ● hypertension ● baseline eGFR, dipstick proteinuria
	Median: 6.1y	Validated 168-item FFQ	●Incident CKD, defined as eGFR<60 mL/min per 1.73 m^2 ●eGFR assessed with MDRD equation	T3 vs T1 OR (95% CI) = 1.46 (1.03; 2.09)*	● age, sex ● BMI ● smoking ● PA ● total energy intake ● diabetes ● hypertension
	Median: 21.0y	Semiquantitative 66-item FFQ	●Incident CKD, defined as 1) eGFR <60 mL/min per 1.73 m^2 accompanied by ≥25% eGFR decline from baseline or 2) kidney disease related hospitalisation or death or 3)ESRD ●eGFR assessed with $CKD\text{-}EPI_{creatinine}$ equation	Q4 vs Q1 HR (95% CI) = 1.13 (1.01; 1.28)*	● age, sex, race-center ● overweight, obesity status ● smoking ● PA ● education ● total caloric intake ● diabetes ● hypertension ● baseline eGFR

Supplemental Table 2 Overview of prospective population-based studies of food and beverage intake and its association with annual change in kidney function.

Food, beverage or dietary pattern	Author, year	Study population, country	Baseline characteristics	Total no.	
Fish	Lee *et al.* 2012	Strong Heart Study in American Indians, USA	●Men: 38% ●Age: 38 ± 16y ●eGFR: 102 ± 26 mL/min per 1.73 m^2 ●Fish intake 0 g/day: 18% >15.0 g/day: 13% ≤15 g/day: 69%	Unknown / 2261	
Milk (products) Low-fat dairy	Herber-Gast *et al.* 2016	Population-based Doetinchem Cohort Study, the Netherlands	●Women: 52% ●Age: 45 ± 10y ●eGFR: 109 ± 14 mL/min per 1.73 m^2 ●Dairy protein intake: 25 ± 10 g/day	3798	
Vegetables	Herber-Gast *et al.* 2017	Population-based Doetinchem Cohort Study, the Netherlands	●Women: 52% ●Age: 45 ± 10y eGFR: 105 ± 14 mL/min per 1.73 m^2 ●Annual eGFR change: -0.95 ± 0.7 mL/min per 1.73 m^2 ●Intake vegetables: 114 [51] g/day	3787	
Fruit	Herber-Gast *et al.* 2017	Population-based Doetinchem Cohort Study, the Netherlands	●Women: 52% ●Age: 45 ± 10y eGFR: 105 ± 14 mL/min per 1.73 m^2 ●Annual eGFR change: -0.95 ± 0.7 mL/min per 1.73 m^2 ●Intake fruit: 150 [153] g/day	3787	

	Follow-up period	Dietary assessment	eGFR assessment	Fully adjusted point estimate (95% CI)	Confounders
	Mean: 5.4y	119-item Block FFQ	MDRD equation	>15 g/day vs 0 g/day Beta (95% CI) = -0.34 (-0.85; 0.18)	● age, sex, center ● WHR ● smoking ● total energy intake ● protein intake, sodium intake ● prevalent diabetes ● TGs ● SBP ● urinary ACR
	Mean: 15.0y	Validated 178-item semiquantitative FFQ	CKD-EPI$_{cystatin-C}$ equation	**Milk (products)** T3 vs T1 Beta (95% CI)= 0.09 (0.002; 0.18)* **Low-fat dairy** T3 vs T1 Beta (95% CI)= 0.11 (0.02; 0.20)*	● age, sex ● BMI ● smoking ● alcohol ● PA ● highest attained level of education ● daily energy intake ● diabetes ● hypercholesterolemia ● hypertension
	Mean: 15.0y	Validated 178-item semiquantitative FFQ	CKD-EPI$_{creatinine-cystatin\ C}$ equation	Q4 vs Q1 Beta (95% CI) = -0.04 (-0.08; 0.07)	● age, sex ● BMI ● smoking ● alcohol use ● time-dependent PA ● education ● daily energy intake ● energy-adjusted intake of total protein, low-fat dairy products, coffee and nuts, supplement use ● diabetes ● hypercholesterolaemia ● hypertension
	Mean: 15.0y	Validated 178-item semiquantitative FFQ	CKD-EPI$_{creatinine-cystatin\ C}$ equation	Q4 vs Q1 Beta (95% CI) = 0.04 (-0.03; 0.11)	● age, sex ● BMI ● smoking ● alcohol use ● time-dependent PA ● education ● daily energy intake ● energy-adjusted intake of total protein, low-fat dairy products, coffee and nuts, supplement use ● diabetes ● hypercholesterolaemia ● hypertension

Supplemental Table 2 continued

Food, beverage or dietary pattern	Author, year	Study population, country	Baseline characteristics	Total no.	
Coffee	Herber-Gast *et al.* 2016	Population-based Doetinchem Cohort Study, the Netherlands	●Men: 48% ●Age: 46 ± 10y eGFR: 108 ± 15 mL/min per 1.73 m^2 ●Annual eGFR change: -1 ± 0.8 mL/min per 1.73 m^2	3786	
Tea	Herber-Gast *et al.* 2016	Population-based Doetinchem Cohort Study, the Netherlands	●Men: 48% ●Age: 46 ± 10y ●eGFR: 108 ± 15 mL/min per 1.73 m^2 ●Annual eGFR change: -1 ± 0.8 mL/min per 1.73 m^2	3786	

*Indicates statistical significant. eGFR, estimated glomerular filtration rate; FFQ, food frequency questionnaire; CKD-EPI, Chronic Kidney Disease Epidemiology collaboration; BMI, body mass index; PA, physical activity.

	Follow-up period	Dietary assessment	eGFR assessment	Fully adjusted point estimate (95% CI)	Confounders
	Mean: 15.0y	Validated 178-item FFQ	CKD-EPI$_{creatinine\text{-}cystatine\ C}$ equation	>6 cups/d vs <1 cups/d Beta (95% CI) = 0.02 (-0.09; 0.14)	● age, sex ● BMI ● smoking ● alcohol use ● PA ● education ● daily energy intake ● energy-adjusted intake of fiber, vitamin C, total protein, fat, saturated fat, tea ● diabetes ● hypercholesterolemia ● hypertension
	Mean: 15.0y	Validated 178-item FFQ	CKD-EPI$_{creatinine\text{-}cystatine\ C}$ equation	>4 vs <1 cups/d Beta (95% CI) = 0.02 (-0.08; 0.11)	● age, sex ● BMI ● smoking ● alcohol use ● PA ● education ● daily energy intake ● energy-adjusted intake of fiber, vitamin C, total protein, fat, saturated fat, coffee ● diabetes ● hypercholesterolemia ● hypertension

Supplemental Table 3 Overview of prospective population-based studies of food and beverage intake and risk of (micro/macro)albuminuria, hyperuricemia.

Food, beverage or dietary pattern	Author, year	Study population, country	Baseline characteristics	No. cases / total no.	
Fish	Lee *et al.* 2012	Strong Heart Study in American Indians, USA	●Men: 38% ●Age: 38 ± 16y ●Fish intake 0 g/day: 18% >15.0 g/day: 13% ≤15 g/day: 69% ●Albuminuria microalbuminuria: 13% macroalbuminuria: 3%	Unknown / 2261	
Fish	Park *et al.* 2019	CARDIA study, USA	●Women: 53% ●Age: 25 ± 4y ●Black: 50% ●eGFR: 124 ± 16 mL/min per 1.73 m^2 ●Fish intake Non-fried fish: 0 ± 0.98 serving/day Fried fish: 0.06 ± 0.27 serving/day	489 / 4133 **number of people with trace elements measured = 3690**	

	Follow-up period	Dietary assessment	Outcome definition + ascertainment	Fully adjusted point estimate (95% CI)	Confounders
	Mean: 5.4y	119-item Block FFQ	●Nephropathy defined as presence of microalbuminuria (urinary ACR=30-299 mg/g) or macroalbuminuria (urinary ACR ≥300 mg/g)	**Albuminuria** >15 g/day vs 0 g/day OR (95% CI) = 1.21 (0.77; 1.92) **Change in urinary ACR** >15 g/day vs 0 g/day Beta (95% CI) = 46.6 (-43.6; 136.9)	● age, sex, center ● WHR ● smoking ● total energy intake ● protein intake, sodium intake ● prevalent diabetes ● TGs ● SBP ● urinary ACR
	Mean: 22.3y	Interview-based dietary history questionnaire	●Incident CKD defined as eGFR <60 mL/min per 1.73 m^2 or albuminuria >30 mg/g (urine ACR) ●eGFR assessed with $CKD\text{-}EPI_{creatinine}$ equation ●Albuminuria determined from a single untimed urine sample	**For n=4133** Every serving per day increment HR (95% CI) = 0.86 (0.73; 1.01) **For n=3690** Every serving per day increment $HR_{without\ adjustment}$ (95% CI) =0.86 (0.73; 1.02) $HR_{with\ adjustment}$ (95% CI) = 0.86 (0.72; 1.02)	**For n=4133** ● age, sex, race study center ● BMI ● current smoker ● alcohol use ● PA ● education ● total energy ● fried fish intake ● personal kidney problems **For n=3690** ● age, sex, race study center ● BMI ● current smoker ● alcohol use ● PA ● education ● total energy ● fried fish intake ● personal kidney problems ● toenail measurements of mercury, cadmium, selenium

Supplemental Table 3 continued

Food, beverage or dietary pattern	Author, year	Study population, country	Baseline characteristics	No. cases / total no.	
Fruit	Wen *et al.* 2018	Village-based Handan Eye Study, China	●Women: 55% ●Age: 50 ± 11y ●ACR: 7 [3;13] mg/g ●Intake fresh fruit Never or rarely: 35% 1-3 times/month: 34% 1-2 times/week: 22% ≥3 times/week: 9%	629 / 3574	
Sugar-sweetened soda	Bomback *et al.* 2010	Community-based ARIC Study, USA	●Women: 55% Age: 54 ± 6y ●Race White: 73% Black: 27% Other: 0.3% ●eGFR: 92 ± 21 mL/min per 1.73 m^2 ●Soda drinking <1 soda/day: 82% 1 soda/day: 12% >1 soda/day: 6%	3288 / 9451	
Diet quality	Chang *et al.* 2013	Community-based CARDIA Study, USA	●Men: 47% ●Age: 35 ± 4y ●African-American race: 41% ●ACR women: 4 [3; 7] ●ACR men: 5 [4; 8]	77 / 2354	

*Indicates statistical significance. HR, hazard ratio; OR, odds ratio; CI, confidence interval; USA, United States of America; eGFR, estimated glomerular filtration rate; PA, physical activity; WHR, waist-hip ratio; ACR, albumin-creatinine; CARDIA, Coronary Artery Risk Development in Young Adults; BMI, body mass index; CVD, cardiovascular disease; SBP, systolic blood pressure; HDL-c, high-density lipoprotein-cholesterol; TG, triglycerides; ARIC, Atherosclerosis Risk in Communities.

	Follow-up period	Dietary assessment	Outcome definition + ascertainment	Fully adjusted point estimate (95% CI)	Confounders
	Median: 5.6y	Self-reported questionnaire	●Albuminuria defined as urinary ACR ≥30 mg/g ●albuminuria assessed with spot urine sample	≥3 times/week vs never or rarely OR (95% CI)= 0.56 (0.38; 0.83)*	● age, sex ● BMI, waist circumference ● smoking ● alcohol use ● PA ● education ● regular consumption of fresh vegetables ● diabetes ● CVD ● total cholesterol, HDL-c, TGs ● hypertension, SBP ● anti-hypertensive drugs ● eGFR, ACR ratio
	Mean: 3.0y	Validated 66-item semiquantitative FFQ	●Incident hyperuricemia defined as serum uric acid >5.7 mg/dl in women and >7.0 mg/dl in men	>1 soda/d vs <1 soda/d OR (95% CI) = 1.17 (0.95; 1.43)	● age, sex, ARIC-field center, race ● BMI ● current tobacco use ● alcohol use ● caffeine intake, animal protein intake ● hypertension ● renal function
	Mean: 15.0y	Validated CARDIA dietary history FFQ	●Incident microalbuminuria, defined as presence of race and sex-adjusted ACR ≥25 mg/g at 2 or more follow-up examinations ●ACRs were obtained from spot urine samples at baseline and follow-up	**Diet quality** Good vs poor OR (95% CI) = 0.50 (0.29; 0.91)*	● age, sex, race ● obesity ● education ● total energy intake ● diabetes ● family history of kidney disease ● hypertension ● baseline ACR

Chapter 3

Association of diet quality with kidney function decline and the interaction with genetic risk in Dutch cardiovascular patients

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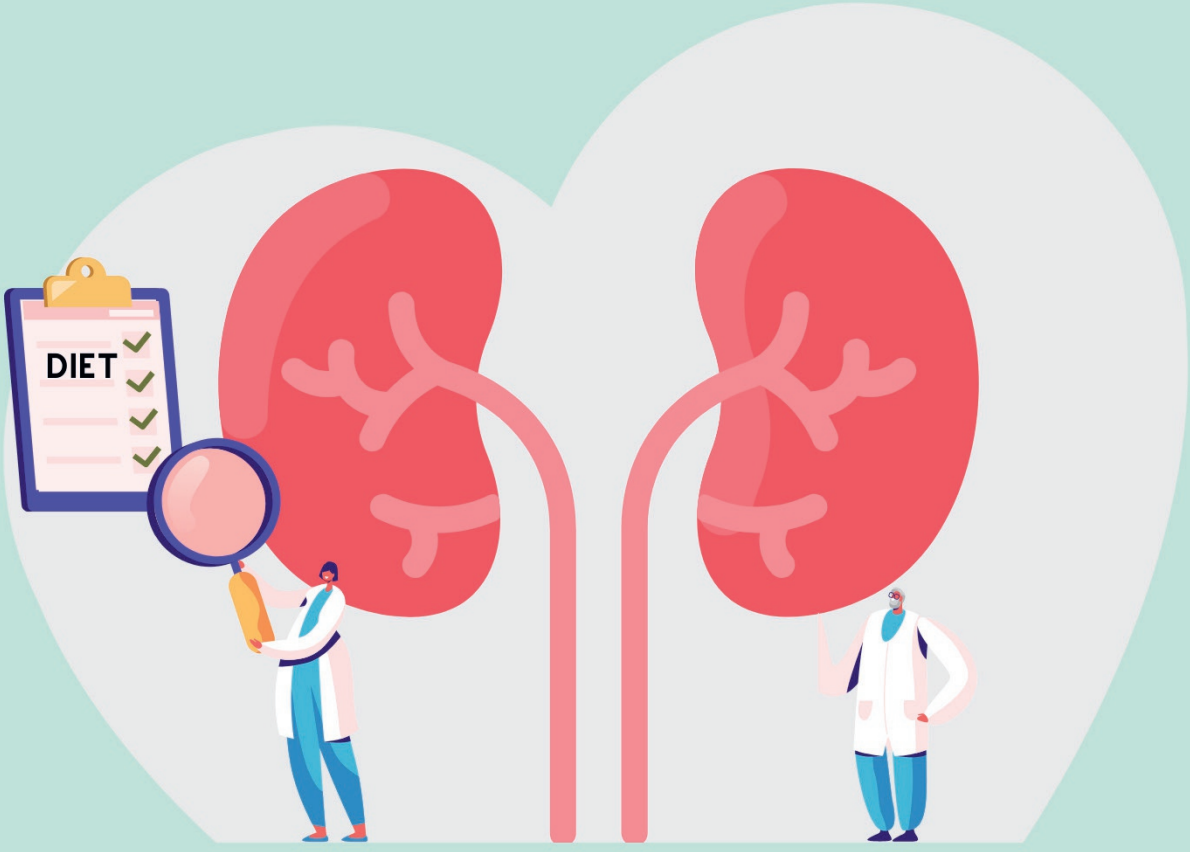

Abstract

Purpose Kidney function decline is accelerated in cardiovascular patients. This study examined the relationship between diet quality and kidney function decline in post-myocardial infarction (MI) patients, and explored differences by genetic risk of chronic kidney disease (CKD).

Methods We used data from 2169 post-MI patients of the Alpha Omega Cohort (aged 60-80 years, 81% male). Habitual dietary intake was assessed at baseline (2002-2006) using a validated 203-item food frequency questionnaire. Diet quality was measured by the Dutch Healthy Diet Cardiovascular Disease (DHD-CVD) index and was based on 16 components of the Dutch dietary guidelines for cardiovascular patients (range total score: 0-160 points). We used the 2021 Chronic Kidney Disease Epidemiology (CKD-EPI) equation to estimate a 40-month change in creatinine-cystatin C-based glomerular filtration rate (eGFR, mL/min per 1.73 m^2). A weighted genetic risk score (GRS) for CKD was calculated using 88 single nucleotide polymorphisms that have previously been linked to CKD. We used linear regression models adjusted for age, sex, education, smoking, physical activity, and medication use, to obtain betas with 95% confidence intervals (CIs) for the association between the DHD-CVD index and annual eGFR change, by GRS.

Results Patients scored, on average, 79 (SD 15) points on the DHD-CVD index. The median eGFR at baseline was 87 (IQR 71, 100), which declined with 1.71 (SD 3.86) mL/min per 1.73 m^2 per year. In multivariable models, the DHD-CVD index was not associated with annual eGFR change (per 1-SD increment in adherence score: -0.09 [95% CI -0.26,0.08]). Better adherence to guidelines for nuts and red meat was associated with less annual eGFR decline (per 1-SD increment in adherence score: 0.17_{nuts} [-0.004,0.34] and $0.21_{red\ meat}$ [0.04,0.38]), whereas a higher adherence score for legumes and dairy was associated with more annual eGFR decline (per 1-SD increment: $-0.20_{legumes}$ [-0.37,-0.04] and -0.18_{dairy} [-0.34,-0.01]). Generally similar results were obtained in strata of GRS.

Conclusion The DHD-CVD index was not associated with kidney function decline after MI, and also not in strata of genetic CKD risk. The preferred dietary pattern for CKD prevention in CVD patients warrants further research.

Introduction

Chronic kidney disease (CKD) is a major public health problem worldwide (1, 2), and it is expected to be the fifth cause of death by the year 2040 (3). Glomerular filtration rate (GFR) is commonly used to assess kidney function, which declines with, on average, 1.0 mL/min per 1.73 m^2 per year in healthy populations (4). In cardiovascular disease (CVD) patients, kidney function decline is at least twice as high (5, 6), meaning they are at higher risk of CKD. We previously observed that post-myocardial infarction (MI) patients with an eGFR of 30-59 mL/min per 1.73 m^2 had a 2-3-fold higher risk of premature mortality from CVD or other causes than patients with an eGFR >90 mL/min per 1.73 m^2 (7). For patients with an eGFR <30 vs >90 mL/min per 1.73 m^2, the risk of (CVD) mortality was 4-6-fold higher (7). A healthy lifestyle, which includes diet, could be important for CKD prevention in CVD patients.

Diet quality scores that reflect adherence to international or national dietary guidelines are widely used in research. In the Netherlands, the Health Council released food-based dietary guidelines in 2015 for chronic disease prevention in the general population (8), that are also reflected in The Dutch Healthy Diet index (DHD15-index) (9). These 2015 dietary guidelines have recently been optimised for CVD patients by the Dutch Health Council (10). Based on these, we calculated a Dutch Healthy Diet Cardiovascular Disease (DHD-CVD) index. Whether overall diet quality may protect against kidney function decline among CVD patients is less clear. To date, only the CORDIOPREV trial has examined the effects of healthy dietary patterns on reducing kidney function decline in stable CVD patients (11). They observed that 5-year consumption of a Mediterranean diet rich in extra-virgin olive oil produced less eGFR decline than a low-fat diet rich in complex carbohydrates (11). However, these dietary patterns were not specifically designed for CVD patients.

Apart from diet and lifestyle, genetic predisposition also contributes to the incidence of CKD (12). So far, 308 single nucleotide polymorphisms (SNPs) have been identified to be associated with CKD in a large genome-wide association study (GWAS) (13). It is Less is known whether diet quality is associated with kidney function decline in CVD patients with a high genetic risk of CKD. In this study, we examined the DHD-CVD index in relation to kidney function decline in CVD patients, and whether this association differed by genetic risk of CKD.

Methods

Study design and study population

The present analysis included data from the Alpha Omega Cohort, which is a prospective cohort study of 4837 Dutch patients (aged 60-80 years old, ~80% male) with a history of MI. At baseline (2002-2006), data were collected on demographic factors, lifestyle, medical history,

health status, and habitual diet (14). Blood samples were collected at baseline (all patients) and after ~40 months of follow-up (60% of the patients), from which serum creatinine and serum cystatin C were measured, amongst other measurements. The patients provided written and oral informed consent, and the study was approved by the medical ethics committee of the Haga Hospital (The Hague, the Netherlands) and by the ethics committees of participating hospitals.

For the current study, patients were eligible if they had a blood sample at baseline and after 40 months of follow-up (n=2488). After exclusion of patients without serum cystatin C and/or serum creatinine measurements at baseline and/or at follow-up (n=148), incomplete dietary data (n=164), and with implausibly high or low energy intakes (<800 or >8000 kcal/day for men, <600 or >6000 kcal/day for women; n=7), 2169 patients were left for analyses of the association between DHD-CVD index and kidney function decline. Of these 2169 patients, 43 patients had no genetic data available, yielding 2126 patients for analyses of the association between DHD-CVD index and kidney function decline in strata of genetic risk of CKD (**Supplemental Fig. 1**).

Dietary assessment

Baseline dietary intake was assessed using a validated 203-item semi-quantitative food frequency questionnaire (FFQ) (15). Food group intake, macronutrients or micronutrients, and energy intake were calculated based on the 2006 Dutch Food Composition Table (NEVO 2006), which was most recent at the time of exposure (2002-2006).

DHD-CVD index

The Dutch Health Council established dietary guidelines for the general population in 2015 (8), from which the DHD15-index was constructed including 15 components (9). The Dutch Health Council recently defined specific dietary guidelines for CVD patients (10). Building upon the DHD15-index, we developed the DHD-CVD index. The fish component was adjusted by assigning a maximum score of 10 points to patients who consumed at least 1.5 portions of fish (any type) per week. An additional component was added for the use of cholesterol-lowering plant sterol or stanol-enriched products, and use of any amount of these products was awarded the maximum score. The DHD-CVD index includes a total of 16 components, with a theoretical range of 0 to 160 points. Higher scores correspond to greater adherence to the guidelines and better diet quality. An overview of the components and their cut-off and threshold values are provided in **Supplemental Table 1**. In **Supplemental Table 2**, an overview of products that were included for each DHD-CVD component is shown. In general, the scoring system, the food groups, chosen cut-offs and threshold values, were all based on the procedures defined by Looman et al. (9).

In the present study, the coffee component was omitted from the DHD-CVD index because type of coffee (filtered or unfiltered) was not assessed in the Alpha Omega Cohort. This resulted in a theoretical score between 0 and 150 points.

Kidney function assessment

At baseline and after ~40 months of follow-up, serum creatinine and serum cystatin C were measured in stored blood samples in a central laboratory (16, 17). Serum cystatin C was measured using a particle-enhanced immunonephelometric assay, and serum creatinine was assessed using the modified kinetic Jaffé method as described in detail elsewhere (7). GFR was estimated using the 2021 equation of the Chronic Kidney Disease Epidemiology (CKD-EPI) Collaboration which includes both serum creatinine and serum cystatin C (18). The outcome was annual eGFR change, which we calculated by subtracting the patients' baseline eGFR from the eGFR at follow-up and dividing the result by the patients' specific follow-up time in years. Negative values represent kidney function decline and positive values represent kidney function increase. Prevalent CKD was defined as eGFR <60 mL/min per 1.73 m^2 at baseline.

Genetic data

We obtained individual-level imputed data on genetic variants. Patients were genotyped using the Global Screening Array (GSA) (19). Genotype imputation was performed using the 1000 Genomes Project reference panel (20).

We calculated two separate weighted genetic risk scores (GRSs) of CKD based on SNPs associated with CKD as reported by a recent large-scale genome-wide association study (GWAS) (13). The main GRS consists of SNPs that were both nominally ($p<0.05$) and genome-wide significantly ($p<5*10^{-8}$) associated with CKD (GRS_all) in this GWAS. We also calculated a sub-score for genetic risk (GRS_sub), which consists of SNPs that were only genome-wide significantly associated with CKD. In general, we calculated a weighted GRS of CKD by generating the sum of the number of risk alleles present at each locus and weighing by the log of the odds for that locus among 2126 patients of the Alpha Omega Cohort. The selection process of SNPs included in both GRS_all and GRS_sub is depicted in **Supplemental Fig. 2**, and the SNPs included in GRS_all and GRS_sub are listed in **Supplemental Table 8**. Briefly, from the GWAS, we first selected SNPs with support for kidney function relevance based on results for blood urea nitrogen as an alternative marker of kidney function (13). We then narrowed the selection by only including nominally and genome-wide significantly associated SNPs. This yielded 119 SNPs in total that were each associated with either a lower or higher risk of CKD in this GWAS (13). Data of 11 SNPs were not available in the Alpha Omega Cohort, and we also excluded 20 ambiguous SNPs, yielding 88 independent non-ambiguous SNPs to be included in GRS_all. Of these 88 SNPs, 16 were previously reported to be genome-wide significantly associated with CKD in this GWAS (13) and were included in GRS_sub. We then compared the SNP effect alleles of the GWAS (13) with the SNP effect alleles in the Alpha

Omega Cohort and harmonised the data accordingly. The effect size belonging to each SNP, as reported by the GWAS, was harmonised in such a way that the interpretation was "higher genetic risk of CKD". The GRS_all ranged between -4.161 to 3.950. GRS_all was divided in tertiles (T1: ≤ -0.434; T2: > -0.434 – ≤0.411; T3: >0.411), with T3 representing the group with a high genetic risk of CKD. The GRS_sub ranged from -3.425 to 3.572. GRS_sub was divided into low and high genetic risk, using the median-split (>-0.00105).

Assessment of covariates

Data on sociodemographic factors, lifestyle habits, and health status at baseline were collected through self-administered questionnaires as described in detail elsewhere (14). The highest attained level of education was categorised as only elementary, low, intermediate, and high. Smoking status was categorised in three groups (never, former, current). The validated Physical Activity Scale for the Elderly was used to assess physical activity (21), and categorised in three groups: low (<3 metabolic equivalent tasks [METs]), intermediate (0-5 days/week moderate or vigorous activity [>3 METs]), and high (≥5 days/week moderate or vigorous activity [>3 METs]). Blood samples were collected by trained research nurses, from which blood lipids (in mmol/L, i.e., total serum cholesterol, high-density lipoprotein cholesterol [HDL-c], and triglycerides) and plasma glucose (mmol/L) were measured using standard kits (Hitachi 912, Roche Diagnostics, Basel, Switzerland). Low-density lipoprotein cholesterol (LDL-c) was calculated using the Friedewald formula (22). Patients with BMI ≥30 kg/m^2 were classified as having obesity. Diabetes mellitus was considered present in case of a self-reported physician's diagnosis, use of glucose-lowering medication, or elevated plasma glucose (≥7.0 mmol/L if fasted >4 hours or ≥11.0 mmol/L if not fasted). Blood pressure (mmHg) was measured twice by trained research nurses at the patients' homes or in the hospital. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured on the left arm with the patient in a seated position using an automated device (Omron HEM-711, Omron Healthcare Europe B.V., Hoofddorp, the Netherlands), and values were averaged. Self-reported medication was coded according to the Anatomical Therapeutic Chemical Classification System (ATC) (23). Codes for antihypertensive medication comprised C02, C03 (C03C for loop diuretics), C08 and C09 (C09A and B for angiotensin-converting enzyme [ACE] inhibitors and C09C and D for Angiotensin II Receptor Blockers [ARBs]). The code for lipid modifying agents was C10.

Statistical analysis

We visually checked the distribution of all baseline variables using histograms and QQ-plots. Baseline characteristics and adherence to dietary guidelines are presented for the total analytical sample and across sex-specific tertiles of the DHD-CVD index. Means ± standard deviations (SDs) were used to describe normally distributed data, medians with interquartile ranges (IQR) were used for skewed variables, and n (%) for categorical data.

Beta coefficients with 95% CIs for the association between the DHD-CVD index and annual eGFR change were obtained from multivariable linear regression models. The DHD-CVD index was analysed per 1-SD increment and in sex-specific tertiles (T1: <77.1; T2: ≥77.1 - <89.2; T3: ≥89.2 for women, and T1: <72.4; T2: ≥72.4 - <84.8; T3: ≥84.8 for men; T1 as reference). We also analysed adherence to guidelines for each individual DHD-CVD component (score) in relation to annual eGFR change, and absolute intake (grams/day) of each DHD-CVD component per 1-SD increment (for vegetables, fruits, whole grains, dairy, fish, tea, liquid fats and oils, and plant sterol or stanol-enriched products) or per 1-SD decrease (for refined grains, solid fats, red and processed meat, sugar-sweetened beverages and fruit juices, alcohol, and sodium intake). Because of low intake, absolute intake of legumes and nuts was analysed in categories (consumers vs non-consumers). For the association of DHD-CVD index with annual eGFR change, we also used restricted cubic splines (RCS, knots located at 10th, 50th, and 90th percentile) in men and women separately to assess potential non-linearity. These associations were visualised in graphs. We further studied the distribution of kidney function-related factors and the DHD-CVD index across genetically proxied CKD. We therefore divided GRS_all in tertiles, and used the median-split for GRS_sub, to compare the sociodemographic factors, lifestyle factors, clinical factors, and kidney function variables across the categories of each GRS. The total DHD-CVD index in relation to kidney function decline was subsequently analysed across categories of genetically proxied CKD risk. Similar analyses were performed for DHD-CVD components, but only among patients at high genetic risk of CKD.

For all analyses, three multivariable models were created. The first two models included confounders, which were selected *a priori* based on previous literature and biological knowledge. The basic model (model one) included age, sex, education level (only elementary, low, intermediate, and high), and total energy intake. In model two, we additionally adjusted for smoking status (never, former, current), physical activity (low, intermediate, and high), use of renin-angiotensin aldosterone system (RAAS) drugs (yes, no), and use of lipid-lowering agents (yes, no). In model three, we additionally adjusted for potential intermediates of the DHD-CVD-kidney association: SBP, BMI, diabetes mellitus, and HDL-c. We used model two as the main model. For analyses of individual DHD-CVD components, we additionally adjusted model two for all other DHD-CVD components. In the genetic analyses, we further adjusted model two for the first three genetic principal components.

The association between the DHD-CVD index and annual eGFR change was repeated in subgroups of patients with and without diabetes, obesity, and CKD. The main analysis was also repeated in a sample without RAAS users and diuretics users because these drugs could improve kidney function and may interact with diet (24-26). We evaluated the robustness of the associations between DHD-CVD components (score and absolute intake) and annual eGFR change in patients with diabetes, obesity, and CKD.

Missing data of covariables were imputed using multiple imputation with chained equations (with 10 imputations and 10 iterations) using the MICE package (27). The analyses were performed in each imputed dataset separately, and the estimates were subsequently pooled using Rubin's rules (28). We used RStudio version 3.6.0 for all analyses, and a two-sided p-value <0.05 was considered statistically significant.

Results

Baseline characteristics and habitual food intake

Baseline characteristics are presented in **Table 1**. The mean ± SD age was 69 ± 5 years, and ~80% of the patients were male. Compared to patients with the lowest diet quality (T1), patients with the highest diet quality (T3) were more often highly educated (16 vs 11%), physically active (29 vs 18%), had lower rates of smoking (10 vs 23%), diabetes (17 vs 19%) and obesity (20 vs 24%), and had higher eGFR values (88 vs 86 mL/min per 1.73 m^2). CKD prevalence was also higher among patients with the highest diet quality vs patients with the lowest diet quality (14 vs 12%).

Adherence to individual dietary guidelines (scores) and absolute intakes (grams/day) of foods and drinks in 2169 post-MI patients and across sex-specific tertiles of the DHD-CVD index are presented in **Table 2**. Patients scored on average 79 ± 15 points on the DHD-CVD index out of a maximum score of 150. Patients adhered best to guidelines for limiting red meat and alcohol intake (median scores of 10 out of 10 points), and least to guidelines for increasing legumes and nuts intake (median scores <2.5 points).

Table 1 Baseline characteristics of 2169 patients of the Alpha Omega Cohort and across sex-specific tertiles of the DHD-CVD index.

		DHD-CVD index, score		
	All patients	T1	T2	T3
		W: <77.1	W: ≥77.1 - <89.2	W: ≥89.2
		M: <72.4	M: ≥72.4 - <84.8	M: ≥84.8
	N=2169	N=723	N=723	N=723
Sociodemographic factors				
Age, y	68.9 ± 5.40	68.2 ± 5.26	69.0 ± 5.42	69.5 ± 5.46
Women, n(%)	417 (19.2)	139 (19.2)	139 (19.2)	139 (19.2)
Education[a], n(%)				
Only elementary	446 (20.7)	171 (23.8)	147 (20.5)	128 (17.7)
Low	779 (36.1)	251 (34.9)	288 (40.2)	240 (33.2)
Intermediate	671 (31.1)	221 (30.7)	213 (29.7)	237 (32.8)
High	263 (12.2)	77 (10.7)	69 (9.6)	117 (16.2)
Lifestyle				
Smoking status, n(%)				
Never	360 (16.6)	90 (12.4)	120 (16.6)	150 (20.7)
Former	1481 (68.3)	466 (64.5)	514 (71.1)	501 (69.3)
Current	328 (15.1)	167 (23.1)	89 (12.3)	72 (10.0)
Physical activity[a], n(%)				
Low	856 (39.6)	322 (44.6)	283 (39.3)	251 (35.0)
Intermediate	807 (37.4)	269 (37.3)	278 (38.6)	260 (36.2)
High	497 (23.0)	131 (18.1)	159 (22.1)	207 (28.8)
Blood lipids[a], mmol/L				
Total serum cholesterol	4.75 [4.19, 5.33]	4.77 [4.22, 5.36]	4.71 [4.16, 5.34]	4.77 [4.18, 5.29]
LDL-cholesterol	2.64 [2.17, 3.17]	2.67 [2.16, 3.20]	2.64 [2.18, 3.15]	2.62 [2.16, 3.16]
HDL-cholesterol	1.21 [1.03, 1.43]	1.21 [1.04, 1.44]	1.19 [1.03, 1.43]	1.21 [1.03, 1.42]
Triglycerides	1.63 [1.21, 2.26]	1.60 [1.25, 2.29]	1.65 [1.21, 2.23]	1.67 [1.18, 2.29]
Other cardiovascular factors				
SBP[a], mmHg	143 ± 21.2	143 ± 21.2	144 ± 21.7	144 ± 20.5
DBP[a], mmHg	81.5 ± 10.7	81.6 ± 10.3	81.4 ± 11.1	81.5 ± 10.6
BMI[a], kg/m^2	27.6 ± 3.61	27.8 ± 3.76	27.7 ± 3.72	27.4 ± 3.33
Obesity[a,b], n(%)	483 (22.3)	175 (24.2)	165 (22.8)	143 (19.8)
Plasma glucose[a], mmol/L	5.46 [4.96, 6.35]	5.55 [5.01, 6.50]	5.41 [4.92, 6.25]	5.42 [4.95, 6.28]
Diabetes mellitus[c], n(%)	394 (18.2)	134 (18.5)	136 (18.8)	124 (17.2)
Kidney function				
eGFR, mL/min per 1.73 m^2	87.0 [71.4, 99.5]	86.0 [71.0, 99.2]	87.6 [72.4, 99.3]	87.6 [70.3, 100.0]
CKD[d], n(%)	273 (12.6)	85 (11.8)	84 (11.6)	104 (14.4)
Serum creatinine, µmol/L	84.0 [72.0, 101.0]	86.0 [73.0, 102.0]	84.0 [71.0, 100.0]	82.0 [71.0, 100.5]
Serum cystatin C, mg/L	0.92 [0.82, 1.10]	0.93 [0.82, 1.10]	0.91 [0.82, 1.00]	0.92 [0.82, 1.10]
Medication use, n(%)				
Antihypertensives	1887 (87.0)	640 (88.5)	627 (86.7)	620 (85.8)
ACE-inhibitors	918 (42.3)	325 (45.0)	300 (41.5)	293 (40.5)
ARBs	287 (13.2)	79 (10.9)	109 (15.1)	99 (13.7)
Diuretics	442 (20.4)	150 (20.7)	140 (19.4)	152 (21.0)
Lipid-lowering agents	1872 (86.3)	621 (85.9)	630 (87.1)	621 (85.9)

Values are means ± SDs for normally distributed variables, medians [IQRs] for skewed variables, or n (%) for categorical variables. [a] Part of the cohort had missing values for education (n=10), physical activity (n=9), total serum cholesterol (n=11), LDL-c (n=108), HDL-c (n=11), triglycerides (n=11), SBP (n=3), DBP (n=3), BMI and obesity (n=2), plasma glucose (n=17). [b] Obesity is defined as BMI ≥30 kg/m^2. [c] Diabetes mellitus is defined as a self-reported physician's diagnosis, use of glucose-lowering medication or elevated plasma glucose (≥7.0 mmol/L if fasted >4 h or ≥11.0 mmol/L if not fasted). [d] CKD is defined as eGFR <60 mL/min per 1.73 m^2. DHD-CVD, Dutch Healthy Diet for cardiovascular disease patients; LDL-c, low-density lipoprotein cholesterol; HDL-c, high-density lipoprotein cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure, BMI, body mass index; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; ACE-inhibitors, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers.

Table 2 Adherence to individual dietary guidelines (scores) and absolute intakes (grams/day) of foods and drinks in 2169 patients of the Alpha Omega Cohort and across sex-specific tertiles of the DHD-CVD index.

		DHD-CVD index[a]		
	All patients	T1 W: <77.1 M: <72.4	T2 W: ≥77.1 - <89.2 M: ≥72.4 - <84.8	T3 W: ≥89.2 M: ≥84.8
	N=2169	N=723	N=723	N=723
Total DHD-CVD score	79.4 ± 14.6	63.4 ± 7.91	79.6 ± 3.93	95.2 ± 7.57
Adherence to individual dietary guidelines				
Vegetables ≥200 g/d, score	4.49 ± 1.95	4.11 ± 1.82	4.47 ± 1.91	4.88 ± 2.05
Fruit ≥200 g/d, score	5.50 [2.14, 10.0]	3.52 [0.83, 6.03]	5.48 [2.51, 10.0]	8.24 [4.97, 10.0]
Grain products, score No consumption of refined cereal products OR Ratio of whole grains to refined grains ≥11	6.65 [5.52, 9.14]	6.26 [4.78, 9.01]	6.58 [5.55, 8.83]	7.22 [5.81, 9.37]
Legumes ≥10 g/d, score	2.18 [0.00, 6.26]	0.00 [0.00, 4.38]	1.27 [0.00, 5.79]	4.40 [0.00, 7.94]
Unsalted nuts ≥15 g/d, score	1.18 [0.00, 1.84]	0.52 [0.00, 1.84]	1.18 [0.00, 1.84]	1.18 [0.52, 4.72]
Dairy 300-450 g/d, score	7.18 [5.00, 10.0]	6.27 [3.54, 9.08]	7.26 [5.20, 10.0]	7.90 [5.87, 10.0]
Fish ≥21 g/d, score	5.31 [2.07, 8.09]	4.46 [0.99, 7.26]	5.19 [1.88, 7.70]	7.26 [3.64, 10.0]
Black or green tea ≥450 g/d, score	3.33 [0.39, 10.0]	1.47 [0.00, 4.17]	3.33 [0.47, 10.0]	8.01 [2.51, 10.0]
Fats and oils, score No consumption of butter, hard margarines and cooking fats OR Ratio of liquid cooking fats to solid cooking fats ≥13	1.45 [0.15, 10.0]	0.36 [0.00, 1.69]	1.34 [0.24, 10.0]	10.0 [1.26, 10.0]
Red meat ≤45 g/d, score	10.0 [8.66, 10.0]	10.0 [7.66, 10.0]	10.0 [9.04, 10.0]	10.0 [9.60, 10.0]
Processed meat 0 g/d, score	5.55 [0.97, 7.34]	3.32 [0.00, 6.23]	5.60 [1.30, 7.19]	6.37 [4.59, 8.22]
Sugar-sweetened beverages and fruit juices 0 g/d, score	3.58 [0.00, 6.87]	2.60 [0.00, 6.09]	3.47 [0.00, 6.78]	4.12 [0.88, 7.36]
Alcohol ≤10 g/d, score	10.0 [5.84, 10.0]	8.99 [0.00, 10.0]	10.0 [7.16, 10.0]	10.0 [8.28, 10.0]
Sodium ≤1.9 g/d, score	8.68 [6.15, 10.0]	7.56 [4.97, 10.0]	8.89 [6.60, 10.0]	9.30 [7.03, 10.0]
Plant sterol or stanol-enriched products, n(%) with 10 points	877 (40.4)	131 (18.1)	276 (38.2)	470 (65.0)
Absolute intake of DHD-CVD components				
Vegetables, g/d	85.3 [63.7, 111.5]	79.2 [54.5, 104.1]	84.5 [65.1, 110.4]	94.8 [72.0, 118.1]
Fruits, g/d	110.0 [42.8, 247.1]	70.3 [16.6, 120.5]	109.5 [50.3, 242.5]	164.9 [99.4, 289.8]
Whole grains[b], g/d	119.8 [88.0, 160.6]	107.4 [77.6, 159.4]	120.1 [88.3, 160.5]	127.1 [89.5, 162.3]
Refined grains, g/d	29.1 [15.2, 53.3]	34.9 [15.7, 63.4]	30.9 [16.1, 54.5]	25.0 [13.6, 44.0]

Table 2 continued

	All patients	DHD-CVD index[a]		
		T1	T2	T3
		W: <77.1	W: ≥77.1 - <89.2	W: ≥89.2
		M: <72.4	M: ≥72.4 - <84.8	M: ≥84.8
	N=2169	N=723	N=723	N=723
Legumes consumers, n(%)	1135 (52.3)	293 (40.5)	364 (50.3)	478 (66.1)
Intake among consumers, g/d	6.2 [4.1, 8.7]	5.1 [3.4, 7.4]	5.8 [4.2, 8.7]	6.8 [4.5, 9.4]
Nut consumers, n(%)	1507 (69.5)	439 (60.7)	506 (70.0)	562 (77.7)
Intake among consumers, g/d	2.6 [1.8, 7.1]	1.8 [0.8, 2.8]	2.5 [1.8, 3.5]	2.8 [1.8, 7.1]
Dairy, g/d	301 [193, 421]	280 [165, 450]	292 [198, 413]	324 [217, 412]
Fish, g/d	11.1 [4.4, 16.7]	9.4 [2.1, 15.2]	10.9 [3.9, 16.2]	15.2 [7.7, 24.2]
Fatty fish, g/d	6.8 ± 9.2	5.3 ± 7.9	6.4 ± 8.4	8.7 ± 10.6
Lean fish, g/d	7.7 ± 8.8	5.8 ± 6.8	7.4 ± 9.1	10.0 ± 9.9
Tea, g/d	150.0 [17.5, 450.0]	66.1 [0.0, 187.5]	150.0 [21.0, 450.0]	361 [113, 450]
Liquid fats, g/d	21.7 [13.5, 33.5]	18.6 [9.2, 30.1]	22.1 [14.1, 32.9]	25.4 [16.0, 37.3]
Solid fats, g/d	8.61 [0.60, 22.1]	17.5 [7.5, 31.7]	9.18 [1.12, 21.2]	1.11 [0.00, 9.82]
Red meat, g/d	37.1 [20.0, 52.4]	42.1 [22.7, 57.9]	37.3 [20.2, 50.3]	31.3 [16.4, 47.2]
Processed meat, g/d	22.3 [13.3, 45.2]	33.4 [18.8, 51.5]	22.0 [14.0, 43.5]	18.2 [8.90, 27.1]
Sugar-sweetened beverages and fruit juices, g/d	160.5 [78.3, 273.5]	185.0 [97.7, 320.7]	163.2 [80.4, 276.9]	146.9 [66.0, 228.0]
Alcohol, g/d	7.9 [1.5, 18.1]	11.4 [1.8, 31.0]	6.9 [1.2, 15.4]	6.5 [1.3, 13.1]
Sodium, mg/d	2222 (659)	2373 (720)	2187 (640)	2107 (583)
Plant sterols/stanol product consumers, g/d	0.00 [0.00, 13.50]	0.00 [0.00, 0.00]	0.00 [0.00, 13.24]	7.50 [0.00, 20.52]
Other				
Energy intake, kcal/day	1875 [1566, 2233]	1974 [1624, 2390]	1835 [1556, 2209]	1825 [1522, 2120]
Protein, g/d	69.2 [58.1, 81.6]	70.4 [58.1, 86.0]	68.3 [57.9, 80.6]	68.1 [58.2, 80.2]
Phosphorus, mg/d	1305 [1088, 1568]	1303 [1059, 1628]	1302 [1075, 1551]	1310 [1121, 1538]
Potassium, mg/d	3194 [2662, 3758]	3130 [2559, 3711]	3152 [2651, 3755]	3288 [2788, 3826]

Values are means ± SDs for normally distributed variables, medians [IQRs] for skewed variables, or n (%) for categorical variables. [a] The total DHD-CVD score in this project does not include coffee. [b] Whole grains also partly included refined grain products, such as brown bread and multigrain bread. DHD-CVD, Dutch Healthy Diet for cardiovascular disease patients.

DHD-CVD index and kidney function decline

In crude analysis, patients in the top tertile of DHD-CVD index score had slightly more kidney function decline (1.85 ± 3.81 mL/min per 1.73 m^2 per year) than patients in the bottom tertile (1.71 ± 4.03 mL/min per 1.73 m^2 per year). After multivariable adjustment, this difference was not statistically significant (model 2, **Table 3** and **Fig. 1**).

After multivariable adjustment, the annual eGFR decline was less when patients adhered to guidelines for sufficient nut consumption and lower intake of red meat (per 1-SD increment in adherence score: 0.17_{nut} [-0.004,0.34] and $0.21_{red\ meat}$ [0.04,0.38], respectively). A higher adherence score for legumes and dairy was associated with more annual eGFR decline (per 1-SD increment: $-0.20_{legumes}$ [-0.37,-0.04] and -0.18_{dairy} [-0.34,-0.01], respectively). Adherence to all other DHD-CVD components was not associated with kidney function decline (**Table 4**). When examining absolute intakes of individual DHD-CVD components, nut and dairy were not significantly associated with annual eGFR decline. Legumes and tea consumption were adversely associated with kidney function decline (yes vs no: $-0.57_{legumes}$ [-0.90,-0.25] and per 1-SD increment in intake: -0.20_{tea} [-0.37,-0.03], respectively). Limiting the intake of red meat (per 1-SD of 23.2 g/d) was associated with 0.20 mL/min per 1.73 m^2 (95% CI 0.03,0.38) less kidney function decline (**Table 4**).

Table 3 The association between the DHD-CVD index per 1-SD increment in adherence score and in sex-specific tertiles and differences in annual eGFR change in 2169 patients of the Alpha Omega Cohort.

		DHD-CVD index			
	Per 1-SD[a] increment in adherence score	T1	T2	T3	P_{trend}
Mean ± SD annual eGFR change	-1.71 ± 3.86	-1.71 ± 4.03	-1.57 ± 3.73	-1.85 ± 3.81	
Model 1[b]	-0.05 (-0.22,0.12)	Ref	0.23 (-0.17,0.63)[e]	-0.03 (-0.43,0.38)	0.89
Model 2[c]	-0.09 (-0.26,0.08)	Ref	0.20 (-0.20,0.61)	-0.08 (-0.49,0.33)	0.71
Model 3[d]	-0.08 (-0.25,0.09)	Ref	0.22 (-0.18,0.62)	-0.07 (-0.48,0.34)	0.73

[a] 1-SD equals 15 points. [b] Adjusted for age, sex (2 categories), education (3 categories), and energy intake. [c] Model 1 plus additionally adjusted for smoking status (3 categories), physical activity (3 categories), lipid-lowering medication use (2 categories), and renin-angiotensin-aldosterone system blockers (2 categories). [d] Model 2 plus additionally adjusted for systolic blood pressure, body mass index, diabetes (2 categories), high-density lipoprotein cholesterol. [e] Beta coefficient (95% confidence interval) obtained from linear regression models (all such values). DHD-CVD index, Dutch Healthy Diet for cardiovascular disease patients; SD, standard deviation; eGFR, estimated glomerular filtration rate.

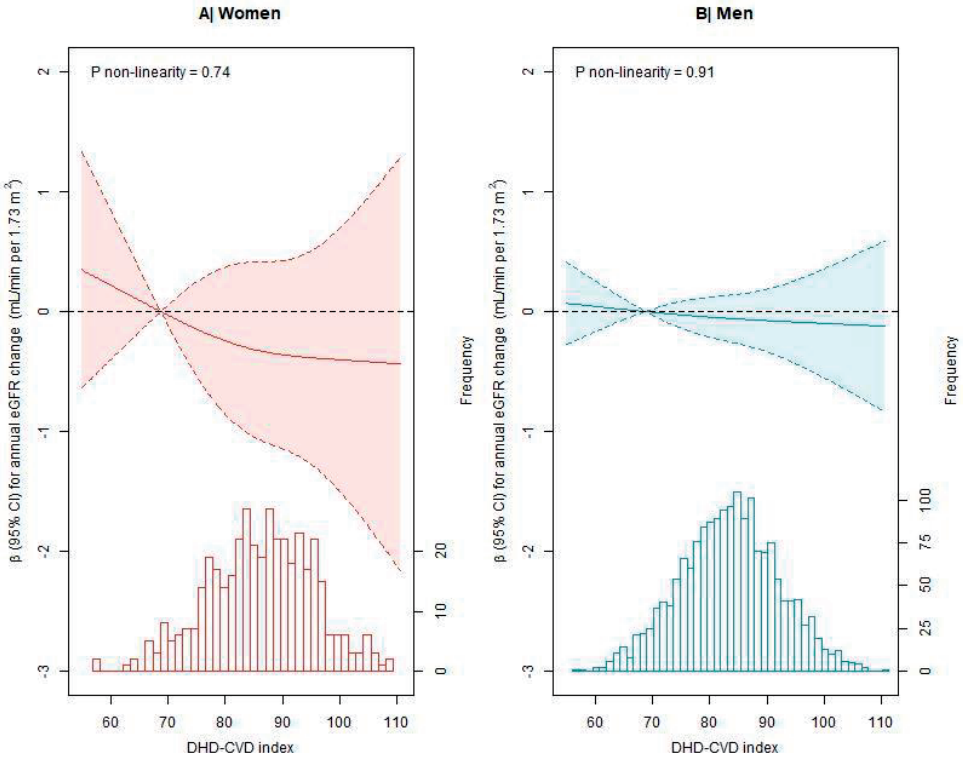

Fig. 1 Continuous associations of the DHD-CVD index with differences in annual eGFR change in female (n=417, panel A) and male (n=1752, panel B) patients of the Alpha Omega Cohort. Solid lines represent beta coefficients and dashed lines represent 95% CIs. The histogram represents the distribution of the DHD-CVD score. Three-knot restricted cubic splines was used, with the median of tertile 1 (69 for women and 64 for men) as reference point. Betas were adjusted for age, education, energy intake, smoking status, physical activity, lipid-lowering medication use, and renin-angiotensin-aldosterone blockers. eGFR, estimated glomerular filtration rate; CI, confidence interval; DHD-CVD index, Dutch Healthy Diet for cardiovascular disease patients.

Table 4 The association between components of the DHD-CVD index[a] and differences in annual eGFR change in 2169 patients of the Alpha Omega Cohort.

	SD	β (95% CI)
Vegetables		
Per 1-SD increment in adherence score[b]	1.95 points	0.02 (-0.15,0.20)
Per 1-SD increment in intake	42.9 g/d	0.003 (-0.17,0.18)
Fruit		
Per 1-SD increment in adherence score[b]	3.59 points	0.08 (-0.10,0.25)
Per 1-SD increment in intake	155 g/d	0.12 (-0.06,0.30)
Grains		
Per 1-SD increment in adherence score[b]	2.54 points	0.02 (-0.15,0.18)
Per 1-SD decrease in refined grains intake	36.7 g/d	-0.04 (-0.26,0.18)
Per 1-SD increment in whole grains intake	59.5 g/d	-0.006 (-0.27,0.25)
Legumes		
Per 1-SD increment in adherence score[b]	3.67 points	-0.20 (-0.37,-0.04)
Consumers (n=1135) vs non-consumers (n=1034)	NA	-0.57 (-0.90,-0.25)
Nuts		
Per 1-SD increment in adherence score[b]	2.52 points	0.17 (-0.004,0.34)
Consumers (n=1507) vs non-consumers (n=662)	NA	0.09 (-0.27,0.46)
Dairy		
Per 1-SD increment in adherence score[b]	3.06 points	-0.18 (-0.34,-0.01)
Per 1-SD increment in intake	242 g/d	-0.12 (-0.32,0.07)
Fish		
Per 1-SD increment in adherence score[b]	3.57 points	-0.07 (-0.24,0.10)
Per 1-SD increment in intake	15.2 g/d	-0.12 (-0.29,0.05)
Consumers (n=1764) vs non-consumers (n=405)	NA	-0.20 (-0.62,0.22)
Tea		
Per 1-SD increment in adherence score[b]	4.06 points	-0.11 (-0.28,0.06)
Per 1-SD increment in intake	258 g/d	-0.20 (-0.37,-0.03)
Fats and oils		
Per 1-SD increment in adherence score[b]	4.41 points	-0.10 (-0.27,0.07)
Per 1-SD increment in liquid fat intake	17.6 g/d	0.13 (-0.09,0.35)
Per 1-SD decrease in solid fat intake	18.3 g/d	-0.17 (-0.38,0.05)
Red meat		
Per 1-SD increment in adherence score[b]	2.01 points	0.21 (0.04,0.38)
Per 1-SD decrease in intake	23.2 g/d	0.20 (0.03,0.38)
Processed meat		
Per 1-SD increment in adherence score[b]	3.25 points	0.01 (-0.18,0.20)
Per 1-SD decrease in intake	21.4 g/d	-0.04 (-0.25,0.17)
Sugar-sweetened beverages and fruit juices		
Per 1-SD increment in adherence score[b]	3.35 points	-0.05 (-0.22,0.12)
Per 1-SD decrease in intake	211 g/d	-0.13 (-0.30,0.06)
Alcohol		
Per 1-SD increment in adherence score[b]	3.90 points	0.11 (-0.07,0.29)
Per 1-SD decrease in intake	15.6 g/d	0.06 (-0.14,0.26)
Sodium		
Per 1-SD increment in adherence score[b]	2.68 points	-0.06 (-0.30,0.19)
Per 1-SD decrease in intake	659 mg/d	-0.004 (-0.36,0.35)
Plant sterols or stanol-enriched products		
Per 1-SD increment in intake	14.1 g/d	-0.08 (-0.42,0.26)
Consumers (n=877) vs non-consumers (n=1292)	NA	-0.05 (-0.23,0.13)

[a] Classification of foods and drinks included in the DHD-CVD index is listed in **Supplemental Table 1**. [b] A higher score means better adherence to the dietary guideline for that specific component. DHD-CVD, Dutch Healthy Diet for cardiovascular disease patients; eGFR, estimated glomerular filtration rate; SD, standard deviation; NA, not applicable.

Diet quality and kidney function decline in strata of genetic CKD risk

The distributions of GRS_all and GRS_sub are shown in **Supplemental Fig. 3**. Generally, diet quality was similar across strata of GRS_all. Patients with a high genetic risk of CKD (T3 of GRS_all), were more often highly educated, had higher rates of smoking, and were less often diabetic and obese, than patients with a low genetic risk of CKD (T1 of GRS_all). On the contrary, patients with a high genetic risk of CKD had higher baseline eGFR values than patients with a low genetic risk of CKD (**Supplemental Table 9**). Baseline values for high education, smoking, and physical activity were similar across groups of GRS_sub (**Supplemental Table 10**). The DHD-CVD index was not associated with kidney function decline in strata of genetic CKD risk (**Table 5**). In 709 patients with a high genetic CKD risk (GRS_all), associations for adherence to guidelines for legumes and dairy and annual eGFR change were no longer present. Results for nut consumption suggested less kidney function decline for consumers vs non-consumers (0.53 [95% CI -0.12,1.19]). For tea, adherence to the guideline was associated with -0.22 mL/min per 1.73 m^2 per year (-0.52,0.08) more kidney function decline. Adherence to the guideline for reducing red meat intake was associated with 0.31 mL/min per 1.73 m^2 per year (0.00,0.61) less kidney function decline (**Supplemental Table 11**).

Table 5 The association between the DHD-CVD index per 1-SD increment in adherence score and differences in annual eGFR change in patients of the Alpha Omega Cohort, stratified by categories of genetic risk of CKD.

	Beta per 1-SD increment in DHD-CVD adherence score	
	GRS_all[a]	GRS_sub[d]
Low genetic risk of CKD		
Range	≥-4.161-≤-0.434	≥-3.425-≤-0.00105
Sample size	N=709	N=1063
Mean ± SD annual eGFR change	-1.87 ± 3.98	-1.73 ± 3.76
Multivariable model[b]	0.05 (-0.26,0.36)[c]	0.003 (-0.24,0.25)
Intermediate genetic risk of CKD		
Range	>-0.434–≤0.411	NA
Sample size	N=708	NA
Mean ± SD annual eGFR change	-1.61 ± 3.64	NA
Multivariable model[b]	-0.07 (-0.35,0.21)	NA
High genetic risk of CKD		
Range	>0.411 – ≤3.950	>-0.00105–≤3.572
Sample size	N=709	N=1063
Mean ± SD annual eGFR change	-1.69 ± 3.91	-1.72 ± 3.93
Multivariable model[b]	-0.15 (-0.47,0.16)	-0.16 (-0.41,0.09)

[a] GRS_all is defined as a genetic risk score based on 88 non-ambiguous SNPs that are both nominally and genome-wide significantly associated with CKD. [b] Adjusted for age, sex, education, energy intake, smoking status, physical activity, lipid-lowering medication use, renin-angiotensin-aldosterone system blockers, and the first three genetic principal components. [c] Beta coefficient (95% confidence interval) obtained from linear regression models (all such values). [d] GRS_sub is defined as a genetic risk score based on 16 non-ambiguous SNPs that are genome-wide significantly associated with CKD. DHD-CVD index, Dutch Healthy Diet for cardiovascular disease patients; SD, standard deviation; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease.

Sensitivity and subgroup analyses

For the total DHD-CVD index, results remained generally similar in subgroups of patients with diabetes, obesity, or CKD (**Supplemental Table 3**) and also after excluding RAAS users or (loop) diuretics users (**Supplemental Table 4**). For individual DHD-CVD components, results varied in several subgroups of patients with diabetes, obesity, or CKD. In 394 patients with diabetes, adherence to guidelines (score) for increasing nut, legumes, and dairy (up to 450 g/d), and limiting red meat intake was no longer statistically significant. Similarly, legumes and nut consumption (yes vs no), higher intake of dairy, and decreasing intake of red meat (grams/day) was also no longer statistically significant (**Supplemental Table 5**). In 484 patients with obesity, results for a higher adherence score for legumes and higher intake of legumes were similar to the results of the main analysis. Results for adherence to guidelines for tea (score) showed an adverse but non-significant association. Higher absolute tea intake was adversely associated with kidney function decline. A higher adherence score for alcohol was associated with 0.46 mL/min per 1.73 m^2 per year (95% CI 0.04,0.87) less kidney function decline. A similar direction of association was observed when examining decrease in alcohol intake (**Supplemental Table 6**). In 273 patients with CKD, higher intake of dairy was adversely associated with kidney function decline and other components were not associated with kidney function (**Supplemental Table 7**).

Discussion

In this prospective cohort study of drug-treated post-MI patients, overall adherence to the Dutch dietary guidelines for CVD patients was not associated with kidney function decline. Similar results were found across strata of genetic CKD risk and in subgroups of patients with diabetes, obesity, or CKD. Of the 15 specific DHD-CVD components that were examined in this study, less annual eGFR decline was observed when patients adhered to guidelines for sufficient nut consumption and low red meat intake. More annual eGFR decline was found when patients adhered to guidelines for legumes and dairy. These results were not materially different in subgroups of patients with diabetes, obesity, or CKD.

Overall diet quality was not associated with kidney function decline in our study of post-MI patients. This remained consistent in subgroups with high genetic CKD risk or after excluding patients with diabetes, obesity, or CKD. In our previous literature review of population-based prospective studies, some, but not all, diet quality indices were associated with a lower incidence of CKD (2). A dietary pattern that was not related with incident CKD after 22 years of follow-up was part of the AHA's Life's Simple 7 and focused on five components (29). Similar to our study, the components fruits and vegetables (≥4.5 servings/day), fish (≥7 ounces/week), fibre-rich whole grains (≥3 ounces/day; ≥1.1 g of dietary fibre/10 g of carbohydrate per day), sodium (<1500 mg/d) and sugar-sweetened beverages (≤36 ounces/week) were not

associated with incident CKD (29). The dietary components and thresholds used to define the DHD-CVD score may not have captured the optimal diet for slowing down kidney function decline in CVD patients.

In contrast to our study, results of the CORDIOPREV and PREDIMED trials showed that adherence to different types of the Mediterranean diet was effective in reducing kidney function decline (11, 30). In the CORDIOPREV trial of CVD patients, the Mediterranean diet supplemented with extra-virgin olive oil was more effective in reducing eGFR decline than a low-fat diet rich in complex carbohydrates after five years of follow-up, particularly among patients with type 2 diabetes and with mildly impaired kidney function (defined as eGFR of 60-90 mL/min per 1.73 m^2) (11). In the PREDIMED trial of elderly participants at higher risk of CVD, two Mediterranean diet types (one supplemented with virgin olive oil and one with mixed nut) were compared against a control low-fat diet after one year of follow-up. The two Mediterranean diet types and the control low-fat diet resulted all in improved kidney function, but without differences in effect between the three diets (30). Higher cut-offs were used for vegetables (≥400 g/d) and fruit intake (≥450 g/d) in the Mediterranean diet of the CORDIOPREV trial (11) than in the DHD-CVD index (≥200 g/d for vegetables and fruit). It is possible that higher intakes of vegetables and fruit are needed to exert beneficial effects on kidney function. Another explanation for our null findings could be related to the consumption of tea or dairy, for which we found a potential adverse association in the current analysis. In the Mediterranean diet, tea and dairy components were not included (11).

Adherence to guidelines for limiting red meat consumption was associated with less kidney function decline. Red meat contains animal protein, which has been associated with accelerated kidney function decline in a previous Alpha Omega Cohort analysis (31). Red meat intake was also associated with a higher incidence of CKD and kidney failure in the population-based ARIC study (median intake: ~0.60 US servings/day; 22 years of follow-up) (32) and the Singapore Chinese Health Study (median intake: ~30 g/d; 15.5 years of follow-up) (33). In our cohort, included foods were steak, pork fillet, and minced meat, and intakes were low (~37 g/d). Although studies in CVD patients are lacking for comparison, our findings suggest that limiting red meat intake could be an important dietary factor for slowing down kidney function decline after MI.

Better adherence to the guideline for nut intake (≥15 g/d) was associated with less kidney function decline in our study. This association was absent when examining nut intake as consumption vs non-consumption. Previous population-based studies also showed potential health benefits of nut consumption on kidney function in US populations (32, 34). Our cohort of post-MI patients consumed nuts with the main meal and as a savoury snack, and included salted and unsalted peanuts, cocktail nuts, cashew nuts, walnuts, and sunflower seeds. The intake of nuts in our cohort was low, only ~6 g/d, whereas the median consumption of nuts

in the ARIC study was about twice as high (32). To the best of our knowledge, similar studies in CVD patients are lacking. We could not adjust for salt intake through nuts, and our results should therefore be interpreted with caution.

In our cohort of post-MI patients, we found an unexpected adverse association for legumes in relation to kidney function decline. This association was also present in patients with diabetes or obesity. Legumes are considered part of a healthy diet, and their consumption is promoted in dietary guidelines. In the ARIC study, legumes were studied in relation to incident CKD (32), showing a beneficial association for the top vs bottom quintile of intake. However, an opposite trend was found in splines analysis (32). In the Singapore Chinese Health Study, the combined intake of legumes and soy was non-significantly associated with a lower risk of kidney failure (33). Studies of legume intake and CKD risk in CVD patients are lacking. In our study, the intake of legumes among consumers was very low (<10 g/d), comprising primarily of canned beans and capuchins, where salt may have been added. In the ARIC study, legumes included fresh, frozen, or canned peas or lima beans and lentils, and the median intake was 0.29 US servings/day (32), which is higher than in our cohort. More research into the type and amount of legume intake in relation to kidney function in CVD patient cohorts is warranted.

In the present analysis, higher dairy intake (g/d) was adversely associated with kidney function decline, particularly in patients who already had CKD at baseline. The DHD-CVD index (in line with the Dutch dietary guidelines) does not distinguish between low-fat and full-fat dairy products, or give recommendations for specific dairy products. In a previous analysis in the Alpha Omega Cohort, we found adverse associations for yoghurt (irrespective of fat content) with kidney function decline (35). Our findings in post-MI patients stand in contrast with findings in general populations, where beneficial associations of dairy with kidney function have been found (2, 36). There are several potential explanations for this discrepancy. Dairy is high in protein, which has been associated with CKD progression and glomerular hyperfiltration in CKD patients (37). Dairy is also a significant source of phosphorus. In individuals with kidney impairment, high phosphorus intake may result in hyperphosphatemia, which can have detrimental effects on kidney function, particularly in patients using phosphate-binding medication (38).

Adherence to the guideline of three daily cups of black or green tea was not associated, and absolute tea intake (grams/day) was adversely associated with kidney function decline in our cohort. This adverse association was even more pronounced in obese patients. Similar adverse associations were observed in a previous analysis of overweight/obese adults with metabolic syndrome of the PREDIMED-Plus study (39). In our study, (caffeinated) black tea was consumed mainly. Black tea has a high concentration of soluble oxalates, about 5 mg/g of tea (40). After binding to calcium, oxalates may form crystals that turn into kidney stones (40,

41). To what extent oxalates could impact the risk of CKD is not clear. More research is needed to conclude whether tea could adversely impact kidney function in (obese) CVD patients.

Strengths of this analysis include a relatively large cohort of stable CVD patients, with detailed data on potential confounders, and the use of an extensive, validated FFQ. Caution is needed with interpreting the findings from sensitivity and subgroup analyses, because we performed many tests, which potentially led to chance findings. Finally, high salt intake is an established risk factor for hypertension and kidney function decline (42, 43), but our FFQ was not a suitable instrument for salt intake because discretionary salt use could not be measured. Further, salt content varies highly across brands of processed foods for which intake could not be accurately assessed. In the Alpha Omega Cohort, no 24-hour urine samples were collected for reliable assessment of sodium intake.

In conclusion, adherence to the Dutch dietary guidelines for CVD patients, as assessed by the DHD-CVD index, did not show an association with kidney function decline in post-MI patients of the Alpha Omega Cohort. This lack of association persisted in patients with a genetic predisposition to CKD. Further research is recommended to identify the relevant food groups and intake ranges that effectively capture the optimal dietary regimen for mitigating kidney function decline in CVD patients.

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Supplemental Table 1 Components and Dutch dietary guidelines of the Dutch Healthy Diet Cardiovascular Disease index (DHD-CVD index) and their threshold (minimum score) and cut-off (maximum score) values (modified from(1)).

Component	Dutch dietary guidelines for CVD patients	Minimum score (=0 points)	Maximum score (=10 points)
Vegetables	Eat ≥200 g/d of vegetables	0 g/d	≥200 g/d
Fruit	Eat ≥200 g/d of fruit	0 g/d	≥200 g/d
Whole grain products[a]	a. Eat ≥90 g/d of whole grain products b. Replace refined cereal products by whole grain products	No consumption of whole grain products OR Ratio of whole grains to refined ≤0.7	No consumption of refined cereal products OR Ratio of whole grains to refined grains ≥11
Legumes	Eat legumes weekly	0 g/d	≥10 g/d
Nuts	Eat ≥15 g/d of unsalted nuts	0 g/d	≥15 g/d
Dairy[b]	Eat a few portions of dairy products daily, including milk or yogurt	0 g/d OR ≥750 g/d	300-450 g/d
Fish	Eat 1-2 servings of fish (any type) weekly	0 g/d	≥21 g/d
Tea	Drink 3 cups of black or green tea daily	0 g/d	≥450 g/d
Fats and oils	Replace butter, hard margarines and cooking fats by soft margarines, liquid cooking fats and vegetable oils	No consumption of soft margarines, liquid cooking fats and vegetable oils OR Ratio of liquid cooking fats to solid cooking fats ≤0.6	No consumption of butter, hard margarines and cooking fats OR Ratio of liquid cooking fats to solid cooking fats ≥13
Red meat	Limit consumption of red meat	≥100 g/d	≤45 g/d
Processed meat	Limit consumption of processed meat	≥50 g/d	0 g/d
Sugar-sweetened beverages and fruit juices	Limit consumption of sugar-sweetened beverages and fruit juices	≥250 g/d	0 g/d
Alcohol	If alcohol is consumed at all, intake should be limited to one Dutch unit (10 g/d ethanol)	Women: ≥20 g/d ethanol Men: ≥30 g/d ethanol	Women and men: ≤10 g/d ethanol
Salt	Limit consumption of table salt to 6 g/d	≥3.8 g/d sodium	≤1.9 g/d sodium
Plant sterol or stanol-enriched products	Consider the use of cholesterol-lowering plant sterol or stanol-enriched products	0 g/d	>0 g/d

[a] This component comprises two sub-components (a and b). Each sub-component has a maximum score of 5 points. [b] Maximum of 40 g cheese can be included.

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Supplemental Table 2 Classification of foods and drinks included in the DHD-CVD index in the Alpha Omega Cohort.

DHD-CVD index components	Food items included
Vegetables	Endive, spinach and purslane, sprouts, cauliflower, broccoli, other cabbages, carrots, peas, broad beans, all sorts of green beans and string beans, leek, chicory, swede, beets, mushrooms, bell pepper, tomatoes, onion, lettuce and raw vegetables, other sorts of vegetables
Fruits	Citrus fruits, apples, pears, bananas, strawberries, blueberries, redcurrant, blackberries, raspberries, cherries, grapes, peaches, nectarines, plums, apricot, kiwi, pineapple, fresh cranberries, melon, mango, papaya, persimmon fruit, passion fruit, lychee, watermelon
Whole grains[a]	Wheat bread, whole wheat bread, malt bread, dark and light rye bread, whole grain bread, whole wheat rye bread, whole raisin bread, whole meal rusks, fiber-rich crispbread, whole crispbread, muesli crispbread, whole wheat cracottes, regular muesli, oatmeal, breakfast product Molenaar, whole wheat macaroni, brown rice
Refined grains	Wasa crispbread, breakfast product All Bran Kellogg's, Brinta, Cornflakes Kellogg's, Rice Krispies Kellogg's, sweetened muesli, raisin bread, white bread, Turkish white bread, croissants, grinded rice, white rice, millet, parboiled rice, wheat bulgur, cooked macaroni, wheat flour
Legumes	(Cooked) capuchins, white beans in tomato sauce, brown beans, dried peas split pesi, cooked white/brown beans, lentils, soybeans, boiled green peas, chickpeas
Nuts	Nuts and seeds with and without the warm meal, i.e. almonds, cashew nuts, hazelnuts, brazil nuts, unsalted peanuts, walnuts, unsalted mixed nuts, sunflower seeds, salted peanuts, nuts
Dairy	Full-fat luxury cheese, reduced fat luxury cheese, cheese with the warm meal, cubes of cheese, 20% fat cheese, 30% fat cheese, regular cheese, other cheese, packaged breakfast yogurt, low-fat/semi-skimmed/full-fat yogurt, custard, other types of yogurt, low-fat/semi-skimmed/full-fat milk, other types of milk, regular low-fat/semi-skimmed/full-fat milk in coffee, buttermilk, low-fat/semi-skimmed/full-fat chocolate milk and yogurt drink, other chocolate milk and yogurt drink, pudding, porridge, ice cream and other ice cream, whipped cream, coffee creamer, low-fat/semi-skimmed coffee milk, evaporated milk/coffee milk powder, unknown coffee milk, other coffee milk, cream with the warm meal
Fish	Fish fingers, plaice, cod, grilled whole herring, codfish, low-fat/semi-skimmed/fatty fish, pollock, tuna, sole, anchovy, trout, pan herring, buckling, canned herring fillet in tomato sauce, salted herring, eel, sardines, salmon, mackerel, herring in sour, halibut
Tea	Green and black tea

Supplemental Table 2 continued

DHD-CVD index components	Food items included
Fats and oils	<u>Liquid cooking fats and oils</u> Different types of Halvarine products, different types of margarine products, Halvarine and margarine products enriched with plant sterols/stanols, tub margarine 70% fat >17 g saturated fatty acids, diet margarine 60 and 70% fat <17 g saturated fatty acids, sunflower oil, corn oil, soybean oil, safflower oil, peanut oil, olive oil, liquid frying fat, tub margarine 70% fat >17 g saturated fatty acids, liquid bake and frying fats 97% fat, liquid margarine 80% fat <17 g saturated fatty acids, <u>Solid cooking fats</u> Tub margarine 80% fat 17-24 g saturated fatty acids, salted and unsalted butter, semi-skimmed butter, stick margarine 80% fat >24 g saturated fatty acids, solid frying fat, solid bake and frying fats, bacon fat
Sugar-sweetened beverages and fruit juices	Alcohol-free beer, orange juice, apple juice, grape juice, grapefruit juice, tomato juice, vegetable juice, other juices, rosehip syrup, coke with caffeine, other soda's, sport drinks, breakfast drinks with fruits, low-fat/semi-skimmed/full-fat chocolate milk, milkshake, yogurt drinks, buttermilk with fruits
Unprocessed red meat	Different types of organ meat, steaks, pork meat, pork fillet, pork ribs, minced meat, sheep
Processed red meat	Prepared organ meat (liver), beef (loin) roulade, blind veal finch, salted beef, pork fricandeau, pork ham slice, cooked liver, liver products, gammon, luncheon meat, bacon, sausage
Alcohol	Pie or cake, beer, low alcohol or alcohol-free beer, advocaat, mixed/longdrinks, strong liquor, pudding, pieces of chocolates, red wine, rosé wine, white wine, sherry, vermouth, port
Sodium[b]	Cooked liver, bacon, unknown types of meat, sausage, mustard
Plant sterol or stanol-enriched products	Halvarine Becel pro.activ, margarine Benecol, Halvarine Benecol light

[a] Foods were classified as whole grain product if they contained at least 25% wholegrain flour. [b] Sodium intake was only estimated from foods, because discretionary salt use could not be assessed by means of the FFQ. Sodium is present in all food items of the FFQ, except for other types of oil, solid deep frying oil, liquid deep frying oil, lard, olive oil, and deep frying oil. The food items mentioned in the table, are the foods that contribute the most to total sodium intake. DHD-CVD, Dutch Healthy Diet for cardiovascular disease patients.

Supplemental Table 3 The association between the DHD-CVD index per 1-SD increment in adherence score and in sex-specific tertiles and differences in annual eGFR change in patients of the Alpha Omega Cohort, stratified by diabetes, obesity, and CKD status.

		DHD-CVD index		
	Per 1-SD increment in adherence score	T1	T2	T3
Diabetes				
No				
Sample size	N=1775	N=589	N=587	N=599
Mean ± SD annual eGFR change, mL/min per 1.73 m^2	-1.56 ± 3.75	-1.57 ± 3.97	-1.41 ± 3.64	-1.69 ± 3.63
Model 2[a]	-0.10 (-0.28,0.09)[b]	Ref	0.22 (-0.22,0.65)	-0.08 (-0.52,0.36)
Yes				
Sample size	N=394	134	136	124
Mean ± SD annual eGFR change, mL/min per 1.73 m^2	-2.40 ± 4.24	-2.36 ± 4.23	-2.26 ± 4.02	-2.60 ± 4.50
Model 2[a]	-0.09 (-0.52,0.34)	Ref	0.21 (-0.84,1.25)	-0.18 (-1.26,0.90)
Obesity				
No				
Sample size	N=1685	N=547	N=558	N=580
Mean ± SD annual eGFR change, mL/min per 1.73 m^2	-1.64 ± 3.83	-1.58 ± 3.98	-1.54 ± 3.77	-1.80 ± 3.75
Model 2[a]	-0.08 (-0.27,0.11)	Ref	0.12 (-0.33,0.58)	-0.14 (-0.60,0.58)
Yes				
Sample size	N=484	N=176	N=165	N=143
Mean ± SD annual eGFR change, mL/min per 1.73 m^2	-1.94 ± 3.93	-2.13 ± 4.14	-1.68 ± 3.58	-2.01 ± 4.06
Model 2[a]	-0.07 (-0.46,0.32)	Ref	0.39 (-0.47,1.24)	0.12 (-0.78,1.03)
CKD				
No				
Sample size	N=1896	N=638	N=639	N=619
Mean ± SD annual eGFR change, mL/min per 1.73 m^2	-1.92 ± 3.81	-1.86 ± 4.00	-1.79 ± 3.63	-2.11 ± 3.80
Model 2[a]	-0.11 (-0.29,0.07)	Ref	0.15 (-0.27,0.57)	-0.19 (-0.63,0.24)
Yes				
Sample size	N=273	N=85	N=84	N=104
Mean ± SD annual eGFR change, mL/min per 1.73 m^2	-0.27 ± 3.87	-0.64 ± 4.12	0.09 ± 4.08	-0.25 ± 3.47
Model 2[a]	0.19 (-0.31,0.68)	Ref	0.77 (-0.43,1.97)	0.45 (-0.71,1.60)

[a] Adjusted for age, sex, education, total energy intake, smoking status, physical activity, lipid-lowering medication use and renin-angiotensin-aldosterone system blockers. [b] Beta coefficient (95% confidence interval) obtained from linear regression models (all such values). DHD-CVD, Dutch Healthy Diet for cardiovascular disease patients; SD, standard deviation; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease.

Supplemental Table 4 The association between the DHD-CVD index per 1-SD increment in adherence score and in sex-specific tertiles and differences in annual eGFR change in patients of the Alpha Omega Cohort who do not use RAAS or (loop)-diuretics medication.

		DHD-CVD index		
	Per 1-SD increment in adherence score	T1	T2	T3
No RAAS users				
Sample size	N=985	N=325	N=323	N=337
Mean ± SD annual eGFR change, mL/min per 1.73 m^2	-1.31 ± 3.68	-1.26 ± 3.95	-1.17 ± 3.57	-1.48 ± 3.51
Model 2[a]	-0.13 (-0.38,0.11)[b]	Ref	0.15 (-0.43,0.73)	-0.14 (-0.74,0.45)
No diuretics users				
Sample size	N=1727	N=573	N=583	N=571
Mean ± SD annual eGFR change, mL/min per 1.73 m^2	-1.62 ± 3.61	-1.64 ± 3.96	-1.53 ± 3.69	-1.70 ± 3.52
Model 2[a]	-0.08 (-0.27,0.10)	Ref	0.13 (-0.30,0.57)	-0.07 (-0.51,0.38)
No loop-diuretics users				
Sample size	N=1860	N=622	N=612	N=626
Mean ± SD annual eGFR change, mL/min per 1.73 m^2	-1.62 ± 3.74	-1.64 ± 3.96	-1.50 ± 3.69	-1.70 ± 3.55
Model 2[a]	-0.08 (-0.26,0.10)	Ref	0.18 (-0.25,0.60)	-0.01 (-0.44,0.42)

[a] Adjusted for age, sex, education, total energy intake, smoking status, physical activity, lipid-lowering medication use and RAAS blockers (but not when RAAS users are excluded). [b] Beta coefficient (95% confidence interval) obtained from linear regression models (all such values). DHD-CVD, Dutch Healthy Diet for cardiovascular disease patients; SD, standard deviation; eGFR, estimated glomerular filtration rate; RAAS, renin-angiotensin-aldosterone system blockers.

Supplemental Table 5 The association between components of the DHD-CVD index[a] and differences in annual eGFR change in 394 patients of the Alpha Omega Cohort with diabetes.

	SD	β (95% CI)
Legumes		
Per 1-SD increment in adherence score[b]	3.55 points	-0.28 (-0.73,0.17)
Consumers (n=197) vs non-consumers (n=197)	NA	-0.65 (-1.50,0.21)
Nuts		
Per 1-SD increment in adherence score[b]	2.24 points	0.32 (-0.19,0.83)
Consumers (n=267) vs non-consumers (n=127)	NA	-0.03 (-0.98,0.92)
Dairy		
Per 1-SD increment in adherence score[b]	3.15 points	-0.11 (-0.54,0.32)
Per 1-SD increment in intake	242 g/d	-0.02 (-0.52,0.48)
Tea		
Per 1-SD increment in adherence score[b]	4.04 points	-0.35 (-0.82,0.11)
Per 1-SD increment in intake	278 g/d	-0.25 (-0.66,0.17)
Red meat		
Per 1-SD increment in adherence score[b]	1.98 points	0.39 (-0.07,0.85)
Per 1-SD decrease in intake	22.9 g/d	0.24 (-0.24,0.71)
Alcohol		
Per 1-SD increment in adherence score[b]	3.71 points	0.04 (-0.46,0.55)
Per 1-SD decrease in intake	16.3 g/d	-0.27 (-0.81,0.26)

[a] Classification of foods and drinks included in the DHD-CVD index is listed in **Supplemental Table 1.**[b] A higher score means better adherence to the dietary guideline for that specific component. DHD-CVD, Dutch Healthy Diet for cardiovascular disease patients; eGFR, estimated glomerular filtration rate; MI, myocardial infarction; SD, standard deviation; NA, not applicable.

Supplemental Table 6 The association between components of the DHD-CVD index[a] and annual eGFR change in 484 patients of the Alpha Omega Cohort with obesity.

	SD	β (95% CI)
Legumes		
Per 1-SD increment in adherence score[b]	3.67 points	-0.33 (-0.70,0.05)
Consumers (n=260) vs non-consumers (n=224)	NA	-0.66 (-1.38,0.06)
Nuts		
Per 1-SD increment in adherence score[b]	1.93 points	0.09 (-0.40,0.57)
Consumers (n=308) vs non-consumers (n=176)	NA	-0.11 (-0.86,0.65)
Dairy		
Per 1-SD increment in adherence score[b]	3.06 points	-0.04 (-0.40,0.33)
Per 1-SD increment in intake	252 g/d	-0.22 (-0.63,0.18)
Tea		
Per 1-SD increment in adherence score[b]	4.00 points	-0.31 (-0.69,0.07)
Per 1-SD increment in intake	248 g/d	-0.43 (-0.81,-0.05)
Red meat		
Per 1-SD increment in adherence score[b]	2.30 points	0.16 (-0.17,0.49)
Per 1-SD decrease in intake	24.3 g/d	-0.05 (-0.41,0.32)
Alcohol		
Per 1-SD increment in adherence score[b]	3.73 points	0.46 (0.04,0.87)
Per 1-SD decrease in intake	15.0 g/d	0.26 (-0.22,0.74)

[a] Classification of foods and drinks included in the DHD-CVD index is listed in **Supplemental Table 1.**[b] A higher score means better adherence to the dietary guideline for that specific component. DHD-CVD, Dutch Healthy Diet for cardiovascular disease patients; eGFR, estimated glomerular filtration rate; MI, myocardial infarction; SD, standard deviation; NA, not applicable.

Supplemental Table 7 The association between components of the DHD-CVD index[a] and annual eGFR change in 273 patients of the Alpha Omega Cohort with CKD.

	SD	β (95% CI)
Legumes		
Per 1-SD increment in adherence score[b]	3.73 points	0.02 (-0.45,0.49)
Consumers (n=139) vs non-consumers (n=137)	NA	-0.44 (-1.39,0.50)
Nuts		
Per 1-SD increment in adherence score[b]	2.40 points	0.37 (-0.13,0.88)
Consumers (n=178) vs non-consumers (n=98)	NA	0.69 (-0.37,1.75)
Dairy		
Per 1-SD increment in adherence score[b]	3.01 points	-0.18 (-0.67,0.30)
Per 1-SD increment in intake	214 g/d	-0.68 (-1.33,-0.04)
Tea		
Per 1-SD increment in adherence score[b]	4.04 points	-0.23 (-0.72,0.25)
Per 1-SD increment in intake	265 g/d	-0.27 (-0.74,0.20)
Red meat		
Per 1-SD increment in adherence score[b]	2.05 points	0.32 (-0.15,0.79)
Per 1-SD decrease in intake	23.8 g/d	0.17 (-0.32,0.67)
Alcohol		
Per 1-SD increment in adherence score[b]	3.14 points	0.53 (-0.10,1.16)
Per 1-SD decrease in intake	11.6 g/d	0.63 (-0.13,1.38)

[a] Classification of foods and drinks included in the DHD-CVD index is listed in **Supplemental Table 1.** [b] A higher score means better adherence to the dietary guideline for that specific component. DHD-CVD, Dutch Healthy Diet for cardiovascular disease patients; eGFR, estimated glomerular filtration rate; MI, myocardial infarction; SD, standard deviation; NA, not applicable.

Supplemental Table 8 Selection of SNPs.

SNPs obtained from GWAS	SNPs available in the Alpha Omega Cohort and not ambiguous (GRS_all)	Genome-wide significant and not ambiguous (GRS_sub)[a]
rs74748843	rs74748843	
rs17413465	rs17413465	
rs1757915	rs1757915	
rs679843	rs679843	
rs11166440	rs11166440	
rs267738	rs267738	
rs4971100	rs4971100	
rs3850625	rs3850625	
rs2808454		
rs2490391	rs2490391	Yes
rs3791221	rs3791221	
rs807624	rs807624	
rs6546869	rs6546869	Yes
rs11123169	rs11123169	Yes
rs11694902	rs11694902	
rs7425436	rs7425436	
rs35472707	rs35472707	
rs187355703		
rs35284526	rs35284526	
rs4666821	rs4666821	
rs7651407	rs7651407	
rs3774726	rs3774726	
rs2289746	rs2289746	
rs9868185	rs9868185	
rs56065557		
rs11919484	rs11919484	
rs9823161	rs9823161	
rs16874073	rs16874073	
rs28817415	rs28817415	Yes
rs12509595	rs12509595	Yes
rs223471		
rs13157326	rs13157326	
rs1362800	rs1362800	Yes
rs11746506	rs11746506	
rs12520984		
rs79760705	rs79760705	
rs72759880	rs72759880	
rs2010352	rs2010352	
rs12163971	rs12163971	
rs11743174	rs11743174	
rs3812036	rs3812036	Yes
rs3765502		
rs144100226		
rs13200335		
rs77915916		
rs720989		
rs6458868		
rs3925003		
rs72912510		
rs1857859		
rs7740107		
rs3822939		
rs62435145	rs62435145	Yes

Supplemental Table 8 continued

SNPs obtained from GWAS	SNPs available in the Alpha Omega Cohort and not ambiguous (GRS_all)	Genome-wide significant and not ambiguous (GRS_sub)[a]
rs6968554	rs6968554	
rs700753		
rs55773927	rs55773927	
rs801193	rs801193	
rs41301394	rs41301394	
rs6973656	rs6973656	
rs62491533	rs62491533	
rs10254101	rs10254101	Yes
rs34861762	rs34861762	
rs10102889		
rs2039424	rs2039424	Yes
rs1321917		
rs7024579	rs7024579	
rs80282103		
rs7072591	rs7072591	
rs10821905	rs10821905	
rs10821944	rs10821944	
rs7475348	rs7475348	
rs12240572		
rs7095954		
rs2068888	rs2068888	
rs4918943	rs4918943	
rs284859	rs284859	
rs1055256	rs1055256	
rs11564722	rs11564722	
rs963837	rs963837	Yes
rs6484504	rs6484504	
rs61897431	rs61897431	
rs7127946	rs7127946	Yes
rs2727040	rs2727040	
rs1813937	rs1813937	
rs3892895	rs3892895	
rs11237450	rs11237450	
rs10790452	rs10790452	
rs632887	rs632887	
rs117113238	rs117113238	
rs10846157	rs10846157	
rs12313306	rs12313306	
rs1275609	rs1275609	
rs690428	rs690428	Yes
rs11071738	rs11071738	
rs351237	rs351237	
rs4886696		
rs4886755	rs4886755	
rs438339	rs438339	
rs77924615	rs77924615	Yes
rs9932625	rs9932625	
rs62050038		
rs28581385		
rs28735420	rs28735420	
rs2411192		
rs9903801		
rs8866		

Supplemental Table 8 continued

SNPs obtained from GWAS	SNPs available in the Alpha Omega Cohort and not ambiguous (GRS_all)	Genome-wide significant and not ambiguous (GRS_sub)[a]
rs16942751	rs16942751	Yes
rs8096658		
rs7251730	rs7251730	
rs78241494	rs78241494	
rs113445505	rs113445505	
rs17216707	rs17216707	
rs2235826		
rs1407040	rs1407040	
rs4408777	rs4408777	
rs2823139	rs2823139	Yes
rs2834317	rs2834317	
rs4820324		
rs738527	rs738527	

[a] Genome-wide significant SNPs are defined as SNPs with p-value $<10^{-8}$. SNPs, single nucleotide polymorphisms; GWAS, genome-wide association study.

Supplemental Table 9 Baseline characteristics of 2126 patients of the Alpha Omega Cohort across tertiles of GRS_all[a] for CKD.

	Low risk ≤-0.434 N=709	Intermediate risk >-0.434 – ≤0.411 N=708	High risk >0.411 N=709
GRS_all	-1.10 ± 0.56	-0.02 ± 0.24	1.11 ± 0.57
Total DHD-CVD score	79.7 ± 14.4	78.9 ± 15.1	79.8 ± 14.3
Sociodemographic factors			
Education[b], n(%)			
Only elementary	133 (18.8)	152 (21.6)	154 (21.8)
Low	266 (37.7)	255 (36.2)	246 (34.8)
Intermediate	228 (32.3)	217 (30.8)	209 (29.6)
High	79 (11.2)	81 (11.5)	97 (13.7)
Lifestyle			
Smoking status, n(%)			
Never	108 (15.2)	118 (16.7)	125 (17.6)
Former	516 (72.8)	475 (67.1)	463 (65.3)
Current	85 (12.0)	115 (16.2)	121 (17.1)
Physical activity[b], n(%)			
Low	277 (39.3)	282 (40.0)	279 (39.5)
Intermediate	263 (37.3)	267 (37.9)	259 (36.6)
High	165 (23.4)	156 (22.1)	169 (23.9)
Clinical factors			
SBP[b], mmHg	144 ± 21.7	144 ± 19.9	143 ± 21.9
DBP[b], mmHg	82.0 ± 10.6	81.5 ± 10.9	81.1 ± 10.6
BMI[b], kg/m^2	27.7 ± 3.65	27.8 ± 3.60	27.4 ± 3.51
Obesity[b, c], n(%)	161 (22.7)	172 (24.3)	137 (19.3)
Diabetes mellitus[d], n(%)	125 (17.6)	135 (19.1)	122 (17.2)
Kidney function			
2021 eGFR$_{cr\text{-}cysC}$ mL/min per 1.73 m^2	83.8 [69.8, 95.9]	85.6 [69.6, 99.8]	91.1 [75.9, 102.2]
2021 eGFR$_{cr}$ mL/min per 1.73 m^2	79.2 [63.0, 92.7]	81.5 [64.3, 95.2]	87.5 [70.3, 96.1]
2012 eGFR$_{cr}$ mL/min per 1.73 m^2	74.5 [64.4, 85.4]	77.9 [64.6, 87.9]	80.8 [69.5, 89.8]
Serum creatinine, µmol/L	87.0 [75.0, 104.0]	85.0 [71.0, 103.0]	80.0 [68.0, 95.0]
Serum cystatin C, mg/L	0.95 [0.84, 1.10]	0.92 [0.82, 1.10]	0.89 [0.80, 1.00]

Values are means ± SDs for normally distributed variables, medians [IQRs] for skewed variables, or n(%) for categorical variables. [a] GRS_all is defined as a genetic risk score based on 88 non-ambiguous SNPs that are both nominally and genome-wide significantly associated with CKD. [b] Part of the cohort had missing values for education (n=9), physical activity (n=9), SBP (n=3), DBP (n=3), BMI and obesity (n=2). [c] Obesity is defined as BMI ≥30 kg/m^2. [d] Diabetes mellitus is defined as a self-reported physician's diagnosis, use of glucose-lowering medication or elevated plasma glucose (≥7.0 mmol/L if fasted >4 h or ≥11.0 mmol/L if not fasted). GRS, genetic risk score; DHD-CVD, Dutch Healthy Diet for cardiovascular disease patients; SBP, systolic blood pressure; DBP, diastolic blood pressure, BMI, body mass index; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease.

Supplemental Table 10 Baseline characteristics of 2126 patients of the Alpha Omega Cohort across groups of GRS_sub for CKD.

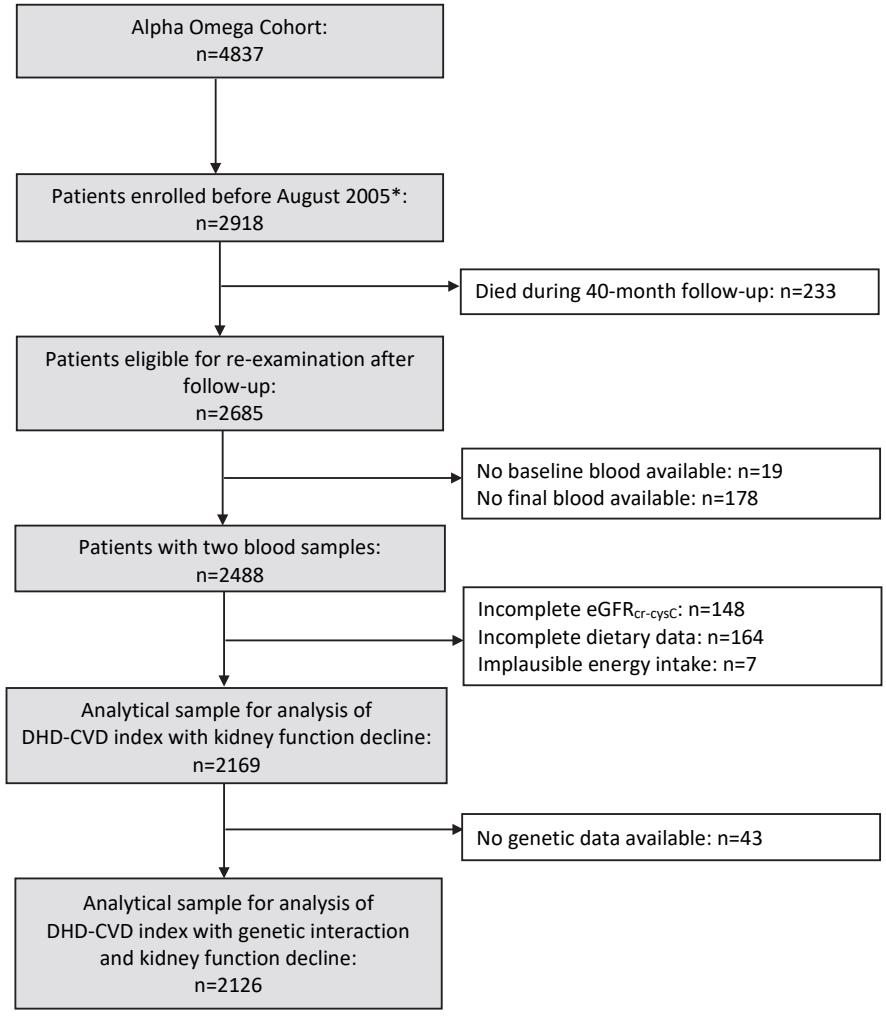
	Low risk: ≤-0.00105 N=1063	High risk: >-0.00105 N=1063
GRS_sub[a]	-0.80 ± 0.58	0.80 ± 0.64
Total DHD-CVD score	79.3 ± 14.4	79.6 ± 14.7
Sociodemographic factors		
Education[b], n(%)		
Only elementary	208 (19.6)	231 (21.9)
Low	399 (37.6)	368 (34.8)
Intermediate	324 (30.6)	330 (31.2)
High	129 (12.2)	128 (12.1)
Lifestyle		
Smoking status, n(%)		
Never	166 (15.6)	185 (17.4)
Former	736 (69.2)	718 (67.5)
Current	161 (15.1)	160 (15.1)
Physical activity[b], n(%)		
Low	407 (38.5)	431 (40.7)
Intermediate	406 (38.4)	383 (36.2)
High	245 (23.2)	245 (23.1)
Clinical factors		
SBP[b], mmHg	143 ± 20.3	144 ± 22.1
DBP[b], mmHg	81.8 ± 10.6	81.2 ± 10.8
BMI[b], kg/m^2	27.7 ± 3.52	27.6 ± 3.66
Obesity[b, c], n(%)	238 (22.4)	232 (21.8)
Diabetes mellitus[d], n(%)	173 (16.3)	209 (19.7)
Kidney function		
2021 eGFR$_{cr\text{-}cysC}$ mL/min per 1.73 m^2	85.2 [70.4, 98.4]	88.5 [72.2, 100.8]
2021 eGFR$_{cr}$ mL/min per 1.73 m^2	80.5 [63.6, 94.5]	84.0 [68.0, 95.5]
2012 eGFR$_{cr}$ mL/min per 1.73 m^2	75.8 [64.6, 86.7]	79.4 [67.5, 88.8]
Serum creatinine, µmol/L	85.0 [73.0, 103.0]	82.0 [70.0, 98.0]
Serum cystatin C, mg/L	0.93 [0.83, 1.10]	0.90 [0.81, 1.00]

Values are means ± SDs for normally distributed variables, medians [IQRs] for skewed variables, or n(%) for categorical variables. [a] GRS_sub is defined as a genetic risk score based on 16 non-ambiguous SNPs that are genome-wide significantly associated with CKD. [b] Part of the cohort had missing values for education (n=9), physical activity (n=9), SBP (n=3), DBP (n=3), BMI and obesity (n=2). [c] Obesity is defined as BMI ≥30 kg/m^2. [d] Diabetes mellitus is defined as a self-reported physician's diagnosis, use of glucose-lowering medication or elevated plasma glucose (≥7.0 mmol/L if fasted >4 h or ≥11.0 mmol/L if not fasted). GRS, genetic risk score; DHD-CVD, Dutch Healthy Diet for cardiovascular disease patients; SBP, systolic blood pressure; DBP, diastolic blood pressure, BMI, body mass index; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease.

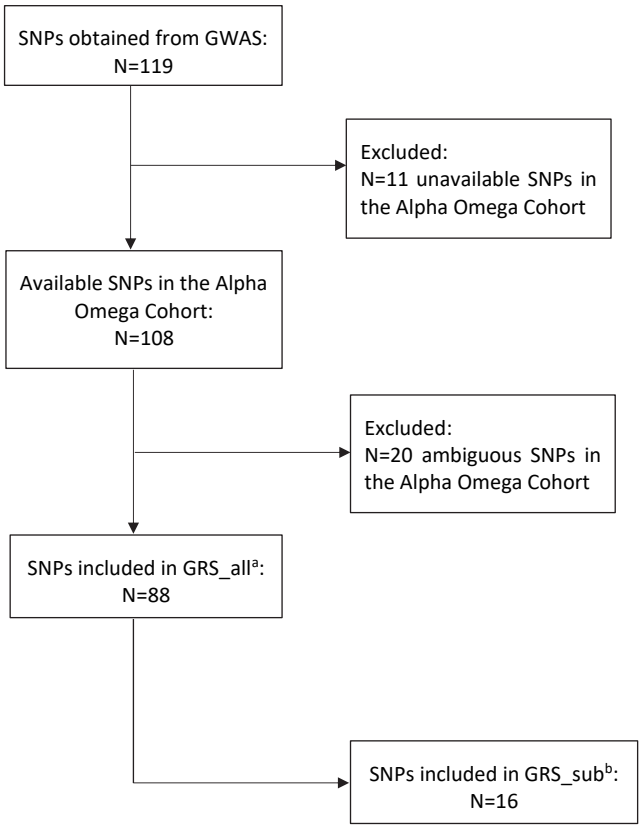
Supplemental Table 11 The association between components of the DHD-CVD index[a] and differences in annual eGFR change in 709 Alpha Omega Cohort patients with a high genetic risk of CKD.

	GRS_all[b]			GRS_sub[c]		
	Sample size	SD	β (95% CI)	Sample size	SD	β (95% CI)
Legumes						
Per 1-SD increment in adherence score[d]		3.69 points	0.03 (-0.27,0.33)		3.64 points	-0.09 (-0.34,0.16
Consumers vs non-consumers	376 vs 333	NA	-0.06 (-0.65,0.53)	551 vs 512	NA	-0.35 (-0.83,0.13)
Nuts						
Per 1-SD increment in adherence score[d]		2.42 points	0.14 (-0.18,0.46)		2.53 points	0.15 (-0.10,0.40)
Consumers vs non-consumers	486 vs 223	NA	0.53 (-0.12,1.19)	725 vs 338	NA	0.08 (-0.44,0.61)
Dairy						
Per 1-SD increment in adherence score[d]		3.08 points	-0.08 (-0.38,0.22)		3.14 points	-0.14 (-0.38,0.10)
Per 1-SD increment in intake		229 g/d	-0.07 (-0.41,0.27)		230 g/d	-0.07 (-0.35,0.21)
Tea						
Per 1-SD increment in adherence score[d]		4.09 points	-0.22 (-0.52,0.08)		4.04 points	-0.12 (-0.37,0.13)
Per 1-SD increment in intake		251 g/d	-0.26 (-0.57,0.06)		256 g/d	-0.16 (-0.41,0.09)
Red meat						
Per 1-SD increment in adherence score[d]		2.00 points	0.31 (0.00,0.61)		2.06 points	0.15 (-0.09,0.39)
Per 1-SD decrease in intake		23.0 g/d	0.33 (0.01,0.65)		23.3 g/d	0.15 (-0.11,0.41)
Alcohol						
Per 1-SD increment in adherence score[d]		4.01 points	0.13 (-0.19,0.45)		3.92 points	-0.02 (-0.29,0.24)
Per 1-SD decrease in intake		15.1 g/d	0.10 (-0.27,0.48)		15.8 g/d	-0.13 (-0.42,0.17)

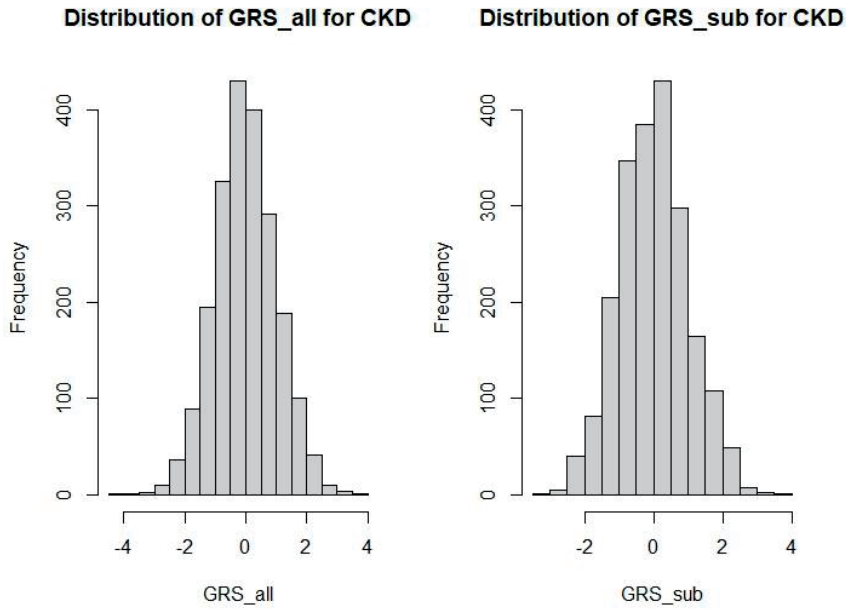
[a] Classification of foods and drinks included in the DHD-CVD index is listed in **Supplemental Table 1.** [b] GRS_all is defined as a genetic risk score based on 88 non-ambiguous SNPs that are both nominally and genome-wide significantly associated with CKD. Within GRS_all, high genetic risk is defined as scores ≥0.411. [c] GRS_sub is defined as a genetic risk score based on 16 non-ambiguous SNPs that are genome-wide significantly associated with CKD. Within GRS_sub, high genetic risk is defined as scores >-0.00105. [d] A higher score means better adherence to the dietary guideline for that specific component. DHD-CVD index, Dutch Healthy Diet for cardiovascular disease patients; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; SD, standard deviation.



Supplemental Fig. 1 Flowchart for selection of the analytical sample of the Alpha Omega Cohort. *Due to financial constraints, only these patients were eligible for follow-up measurements. $eGFR_{cr\text{-}cysC}$, estimated glomerular filtration rate based on creatinine and cystatin C.



Supplemental Fig. 2 Flowchart for selection process of SNPs included in the GRS. [a] GRS_all includes both SNPs that are nominally significantly associated with CKD ($p<0.05$) and SNPs that are genome-wide significantly associated with CKD ($p<10^{-8}$). [b] GRS_sub only includes SNPs that are genome-wide significantly associated with CKD. GWAS, genome-wide association study; SNPs, single nucleotide polymorphisms; GRS, genetic risk score; CKD, chronic kidney disease.



Supplemental Fig. 3. Distributions of GRS for CKD among 2126 patients of the Alpha Omega Cohort. GRS_all ranges from -4.161 to 3.950 and GRS_sub ranges from -3.425 to 3.572. GRS_all, genetic risk score based on 88 non-ambiguous SNPs that are both nominally and genome-wide significantly associated with CKD; GRS_sub, genetic risk score based on 16 non-ambiguous SNPs that are only genome-wide significantly associated with CKD; CKD, chronic kidney disease; SNP, single nucleotide polymorphism.

Part B

Coffee, dairy and kidney function

Chapter 4

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

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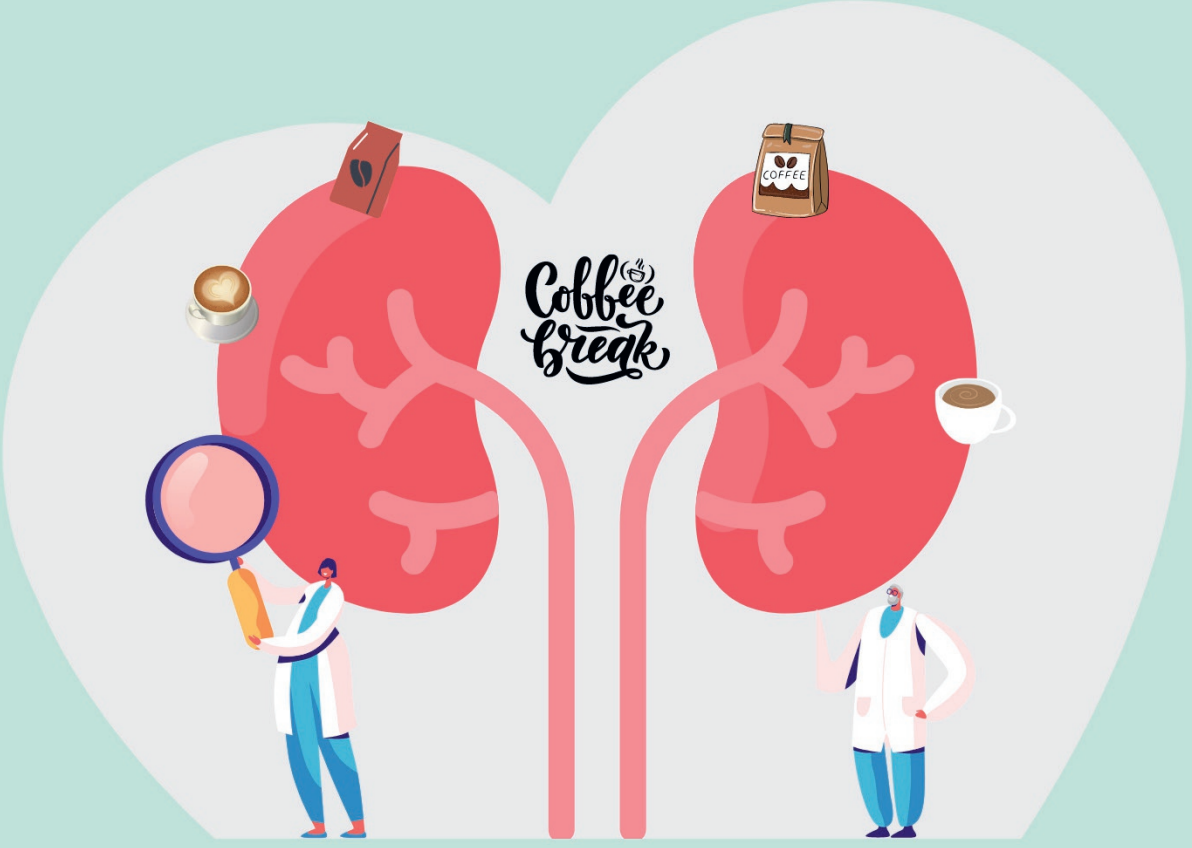

Abstract

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 7914 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^2, 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 analysed 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^2. In the total study population, coffee was not associated with longitudinal eGFR during a median of 5.4 years of follow-up (β = 0.04 mL/min per 1.73 m^2 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^2 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.

Introduction

Chronic kidney disease (CKD) is a long-term condition characterised by progressive kidney function decline with an estimated global prevalence of 13% (1). Despite medical prevention strategies, 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 = 3798; 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 ≥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.

Materials and methods

Study design and study population

We used data from 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 7983 participants aged ≥55 years were enrolled (RS-I). During 2000-01, another 3011 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 3932 participants aged ≥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 1415 RS-I participants who died before the start of RS-I-3, baseline of the current study. Of the remaining sample, 8718 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 8671 participants with available coffee intake data. Of this group, 7914 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^2. The final analytical sample size for this analysis was 4649. 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 2505 (**Fig. 1**). The RS 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.

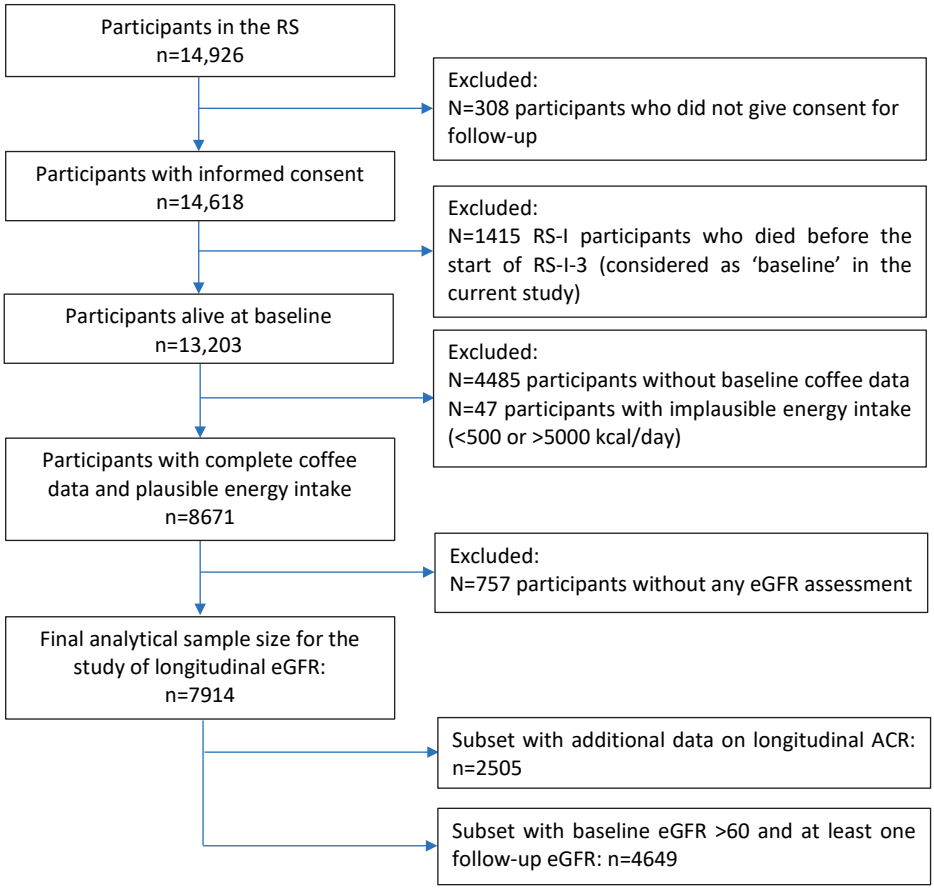

Fig. 1 Flowchart describing the population for analysis. RS, Rotterdam Study; Kcal, kilocalorie; eGFR, estimated glomerular filtration rate; ACR, albumin-to-creatinine ratio.

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.

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, ≥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^2 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.

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 centre. Body mass index (BMI, in kg/m^2) was calculated as weight (kg) divided by height (meters) squared. Blood lipids (mmol/L) were analysed in fasting blood samples, using the cholesteroloxidase-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 ≥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] ≥140 mmHg or diastolic blood pressure [DBP] ≥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 (≥7.0 mmol/L if fasted or ≥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).

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 analysed 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 categorised 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_{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 (two categories), highest level of attained education (four categories) and sub-cohort (three categories). Model two was additionally adjusted for lifestyle and dietary factors, including

smoking status (three 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 [kg/m^2]) and blood pressure lowering drug use (two categories), because these variables could be confounders, but also mediators (25).

Additional analyses
To investigate to what extent CKD risk factors modified coffee's association with longitudinal eGFR, predefined subgroup analyses stratified by age (≤60, >60-70, >70 y), sex, smoking status (never, former, current), BMI (≤25, >25-30, >30 kg/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 three.

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*IQR) and eGFR (mean + 4*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.

Results

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 m^2. More than 50% of the individuals had hypertension, and 10% had T2D or CVD. BMI was 27 (4) kg/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**.

Coffee consumption and kidney function

The mean eGFR declined on average with 4.92 mL/min per 1.73 m^2 over a median of 5.4 years of follow-up. The total number of repeated eGFR assessments was 13,798 (median of two assessments per participant). In the total study population and after adjustment for confounders (model three), coffee was not associated with longitudinally assessed eGFR during follow-up in either continuous analyses (β = 0.04 mL/min per 1.73 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**).

Table 1 Baseline characteristics of 7914 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	7914	279	2026	3423	2186
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]
Sociodemographic factors					
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	3415 (43.2)	97 (34.8)	740 (36.5)	1408 (41.1)	1170 (53.5)
Women	4499 (56.8)	182 (65.2)	1286 (63.5)	2015 (58.9)	1016 (46.5)
Education, n(%)					
Primary	972 (12.3)	29 (10.4)	299 (14.8)	411 (12.0)	233 (10.7)
Intermediate	3181 (40.2)	96 (34.4)	827 (40.8)	1424 (41.6)	834 (38.2)
Higher general	2295 (29.0)	86 (30.8)	564 (27.8)	993 (29.0)	652 (29.8)
University	1399 (17.7)	66 (23.7)	323 (15.9)	558 (16.3)	452 (20.7)
Lifestyle factors					
Smoking status, n(%)					
Never	2474 (31.3)	133 (47.7)	787 (38.8)	1084 (31.7)	470 (21.5)
Former	3771 (47.6)	98 (35.1)	980 (48.4)	1725 (50.4)	968 (44.3)
Current	1655 (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]
Cardiovascular risk factors					
BMI, kg/m^2	27.2 (4.2)	26.7 (4.8)	27.0 (4.1)	27.2 (4.1)	27.4 (4.3)
Overweight, n(%)	3657 (46.2)	121 (43.4)	921 (45.5)	1624 (47.4)	991 (45.3)
Obesity, n(%)	1634 (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(%)	2833 (35.8)	105 (37.6)	753 (37.2)	1198 (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(%)	4926 (62.2)	150 (53.8)	1380 (68.1)	2154 (62.9)	1242 (56.8)
CVD, n(%)	709 (9.0)	18 (6.5)	220 (10.9)	299 (8.7)	172 (7.9)

Table 1 continued

	Total cohort	Coffee consumption (cups/day)			
		0 (non-consumers)	>0 - ≤2 (low intake)	>2 - ≤4 (moderate intake)	>4 (heavy intake)
Medication use, n(%)[a]					
Antihypertensive drugs	2530 (32.0)	86 (30.8)	772 (38.1)	1100 (32.1)	572 (26.2)
Kidney function					
eGFR, mL/min per 1.73 m^2	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 a BMI between 25 and 30 kg/m^2. Obesity is defined as BMI >30 kg/m^2. 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 ≥4h 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. 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. [a] Coded according to the ATC classification system: antihypertensive drugs (C02, C03, C07, C09).

Table 2 Multivariable adjusted associations between coffee consumption and longitudinal eGFR in 7914 participants of the Rotterdam Study.

			Total coffee consumption (cups/day)				
	Continuous		0 (n=279)	>0-≤2 (n=2026)	>2-≤4 (n=3423)	>4 (n=2186)	P_{trend}
	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^2 during follow-up. 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), dietary 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^2) and blood pressure lowering drug use (2 categories).

Coffee-eGFR associations were consistent for both sexes ($P_{interaction}$ = 0.45), but not for different age groups (**Fig. 2**, $P_{interaction}$ <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 m^2 higher eGFR during follow-up (model 3: 0.84 [95% CI 0.51,1.18]; **Fig. 2**). This association became stronger after exclusion of non-coffee drinkers (**Supplemental Table 4**). No significant findings were observed in the younger age groups (**Fig. 2, 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 ($P_{interaction}$ > 0.05; **Fig. 2**), 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. 2, Table 3, Supplemental Table 4**).

Hypertension, CVD, or hypercholesterolemia did not modify the coffee-eGFR association (**Fig. 3**, $P_{interaction}$ >0.05). Among T2D subjects, we observed a trend for coffee with higher eGFR during follow-up (0.42 [95% CI -0.05,0.88]), but the interaction term was not significant ($P_{interaction}$ >0.05, **Fig. 3**). BMI-stratified results showed that among those with BMI >30 kg/m^2, one extra cup of coffee per day was associated with 0.32 mL/min per 1.73 m^2 (95% CI 0.01,0.63) higher eGFR during follow-up (**Fig. 3**). Exclusion of non-coffee drinkers resulted in even stronger associations (**Supplemental Table 4**). Analyses for coffee in categories suggested similar trends (**Table 4**).

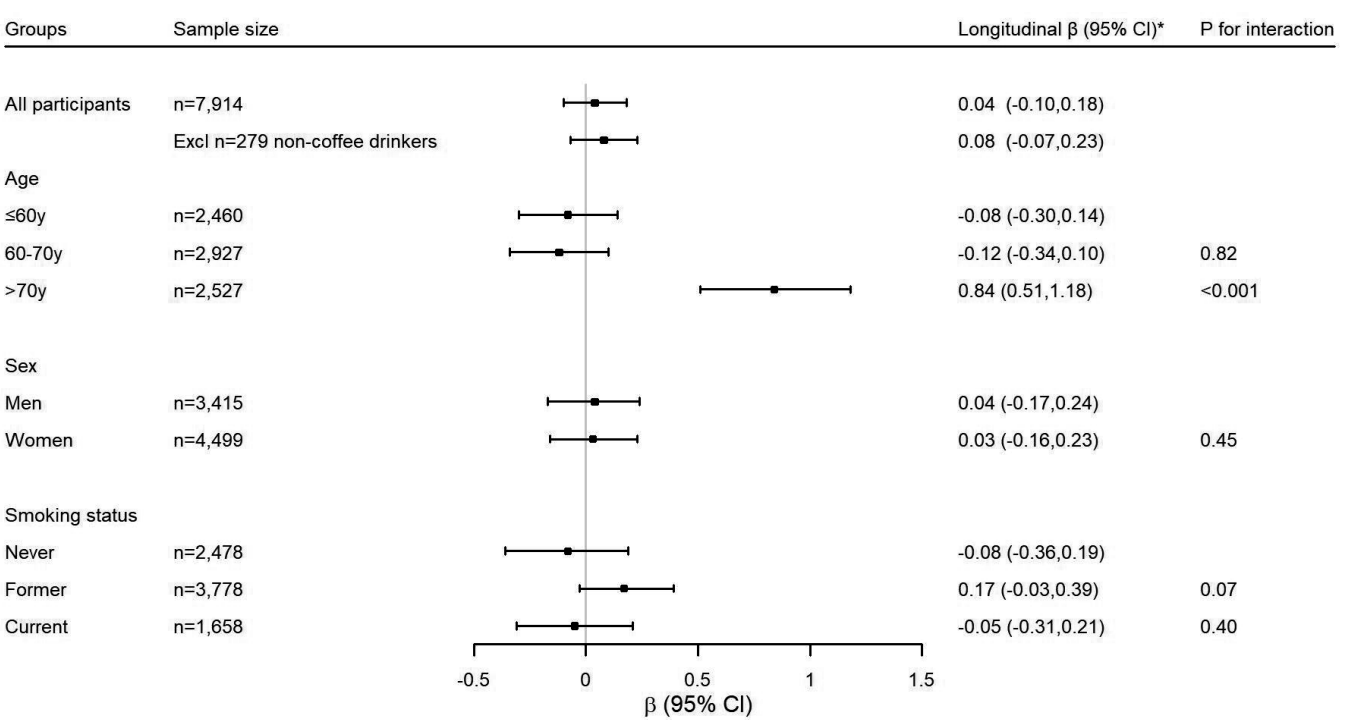

Fig. 2 Changes in longitudinal eGFR during follow-up per one coffee cup/day increase for the total study population, and in subgroups of age, sex and smoking status, among participants of the Rotterdam Study. * Adjusted for: age (except when stratified), sex (2 categories, except when stratified), education (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). eGFR, estimated glomerular filtration rate; CI, confidence interval.

Table 3 Multivariable adjusted associations between coffee consumption and longitudinal eGFR in subgroups of age, sex and smoking status in 7914 participants of the Rotterdam Study.

	Total N	Total coffee consumption (cups/day)								P_{trend}
		0		>0-≤2		>2-≤4		>4		
		β (95% CI)	N	β	N	β (95% CI)	N	β (95% CI)	N	
Age (years)										
≤60	2460	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	2927	1.37 (-1.58,4.32)	70	Ref	647	-1.01 (-2.14,0.12)	1336	-0.54 (-1.81,0.73)	874	0.24
>70	2527	2.55 (-1.42,6.52)	48	Ref	887	2.85 (1.65,4.04)	1181	3.93 (2.28,5.57)	411	0.00
Sex										
Men	3415	2.05 (-0.62,4.72)	97	Ref	740	0.00 (-1.12,1.13)	1408	0.17 (-1.06,1.39)	1170	0.96
Women	4499	0.35 (-1.53,2.23)	182	Ref	1286	-0.01 (-0.86,0.84)	2015	0.36 (-0.69,1.40)	1016	0.65
Smoking status										
Never	2478	0.73 (-1.55,3.01)	133	Ref	787	0.15 (-0.99,1.28)	1087	0.69 (-0.76,2.13)	471	0.47
Former	3778	1.57 (-0.99,4.12)	98	Ref	980	0.36 (-0.61,1.33)	1729	0.56 (-0.59,1.70)	971	0.38
Current	1658	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^2 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^2) and blood pressure lowering drug use (2 categories). eGFR, estimated glomerular filtration rate; N, sample size; CI, confidence interval.

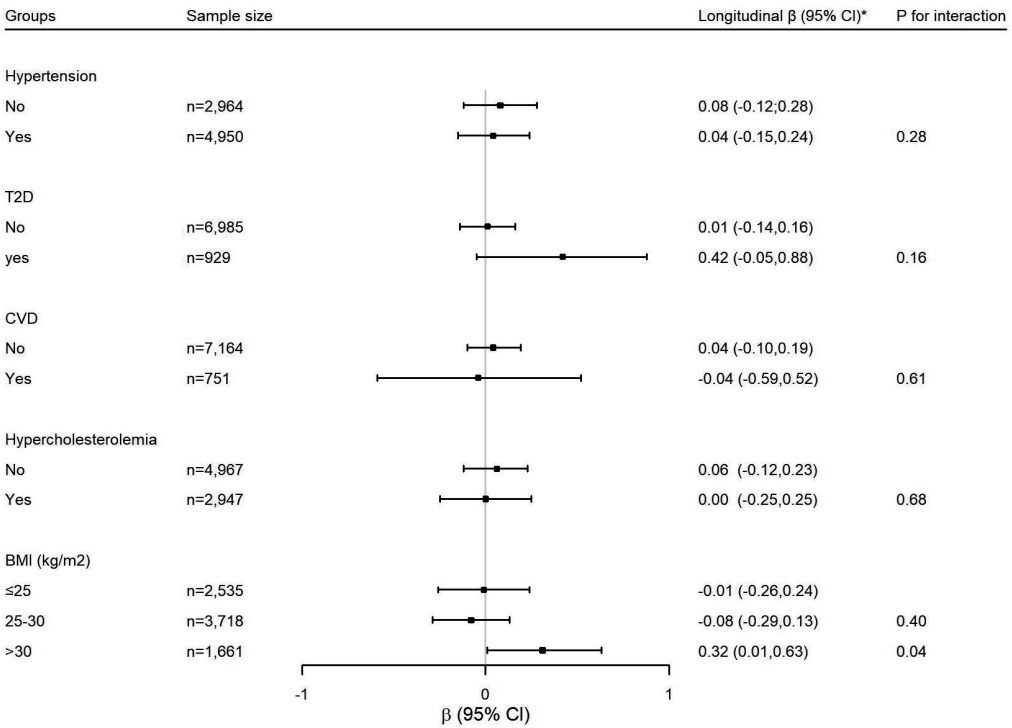

Fig. 3 Changes in longitudinal eGFR during follow-up per one coffee cup/day increase according to subgroups of CKD risk factors, among participants of the Rotterdam Study. *Adjusted for: age, sex (2 categories), education (4 categories), sub-cohort, smoking status (3 categories), physical activity, diet 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). eGFR, estimated glomerular filtration rate; CI, confidence interval; T2D, type 2 diabetes; CVD, cardiovascular disease; BMI, body mass index.

Table 4 Multivariable adjusted associations between coffee consumption and longitudinal eGFR in subgroups of cardiometabolic risk factors in 7914 participants of the Rotterdam Study.

	Total N	Total coffee consumption (cups/day)								P_{trend}
		0		>0-≤2		>2-≤4		>4		
		β (95% CI)	N	β	N	β (95% CI)	N	β (95% CI)	N	
Hypertension										
No	2964	-0.45 (-2.53,1.64)	129	Ref	640	-0.94 (-1.99,0.12)	1257	-0.12 (-1.29,1.05)	938	0.63
Yes	4950	1.91 (-0.31,4.12)	150	Ref	1386	0.52 (-0.37,1.41)	2166	0.65 (-0.41,1.71)	1248	0.24
T2D										
No	6985	0.57 (-1.02,2.16)	254	Ref	1755	-0.16 (-0.87,0.55)	3037	0.14 (-0.68,0.96)	1940	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	7164	0.82 (-0.77,2.40)	258	Ref	1796	-0.15 (-0.86,0.56)	3105	0.19 (-0.63,1.00)	2005	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	4967	1.12 (-0.81,3.06)	172	Ref	1241	0.01 (-0.85,0.88)	2174	0.50 (-0.49,1.50)	1380	0.48
Yes	2947	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/m²)										
≤25	2535	0.83 (-1.70,3.36)	106	Ref	675	-0.00 (-1.19,1.19)	1066	0.21 (-1.18,1.60)	688	0.86
>25-≤30	3718	0.26 (-2.05,2.57)	124	Ref	942	-0.57 (-1.56,0.42)	1647	-0.38 (-1.53,0.76)	1005	0.36
>30	1661	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^2 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^2, 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 ≥4h 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. 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.

In the subset of participants with additional longitudinal ACR data (n = 2505), 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 4312 (median of two 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**).

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 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 three 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_{trend} = 0.07).

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.

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 (≥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.

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 hypothesised that antioxidative 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 hyperglycaemia (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.

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 nonsignificant, 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.

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.

Strengths and limitations

Our study benefited from several strengths. Overall, our study had a large sample size and was community based, which improves generalisability 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 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 generalisability 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.

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: conceptualisation, methodology, software, formal analysis, investigation, writing-original draft, visualisation **COR:** conceptualisation, methodology, software, writing-review & editing, supervision **ACvdB:** writing-review & editing **LC:** writing-review & editing **JMG:** writing-review & editing **EJH:** writing-review & editing **TV:** conceptualisation, methodology, writing-review & editing, supervision.

Conflict of interest

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

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Supplemental Table 1 Baseline dietary intake of 7914 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	7914	279	2026	3423	2186
Dietary factors					
Diet quality score[a]	6.72 (1.88)	7.12 (2.06)	6.96 (1.90)	6.78 (1.88)	6.37 (1.78)
Energy, kcal/day[a]	2130 (613)	2090 (701)	2039 (583)	2112 (586)	2247 (648)
Tea consumption, cups/day	2.40 [1.10, 4.00]	3.60 [1.51, 6.87]	3.00 [1.39, 4.80]	2.79 [1.39, 4.00]	1.39 [0.54, 3.00]
Alcohol consumption, glasses/day[b]	0.64 [0.05, 1.50]	0.09 [0.00, 0.86]	0.36 [0.05, 1.07]	0.64 [0.07, 1.50]	0.71 [0.07, 1.71]
Macronutrients, g/day[a]					
Protein	83.1 [70.4, 97.8]	79.5 [66.2, 94.6]	80.1 [66.8, 94.5]	82.5 [70.6, 95.7]	87.9 [73.5, 104.8]
Carbohydrates	81.0 [63.6, 100.6]	75.0 [60.5, 96.2]	77.2 [60.3, 96.7]	80.7 [63.6, 99.0]	85.6 [67.5, 106.4]
Fats	220 [178, 271]	221 [177, 277]	213 [174, 265]	219 [178, 265]	228 [185, 288]
Micronutrients, mg/day[a]					
Sodium	2241 [1825, 2777]	2221 [1797, 2736]	2138 [1727, 2663]	2212 [1827, 2716]	2408 [1930, 3015]
Potassium	3836 (1072)	3576 (1291)	3612 (1022)	3831 (1017)	4080 (1114)
Magnesium	353 (111)	355 (134)	331 (108)	348 (104)	381 (116)

Normally distributed variables are described in means (standard deviation), skewed variables in median [interquartile range]. N, sample size. [a] Diet quality, energy intake, macronutrients and micronutrients were not measured in RS-I-3. Therefore, RS-I-1 was used as proxy of RS-I-3. A diet quality score (0-14) reflecting adherence to Dutch dietary guidelines, examining the adherence to the following 14 components: vegetables, fruit, whole-grains, legumes, nuts, dairy, fish, tea, ratio whole-grains:total grains, ratio unsaturated fats and oils:total fats, red and processed meat, sugar-containing beverages, alcohol, and salt. A higher score indicates a healthier diet. [b] 10 grams of alcohol equals one standard drink.

Supplemental Table 2 Baseline characteristics of Rotterdam Study participants with and without available coffee data.

	Availability of coffee data	
	Yes (n=7914)[a]	No (n=4485)[a]
Sociodemographic factors		
Age, y	65.5 (9.6)	63.5 (10.5)
Sex, n(%)		
Men	3415 (43.2)	1739 (38.8)
Women	4499 (56.8)	2745 (61.2)
Education, n(%)		
Primary	972 (12.4)	926 (21.1)
Intermediate	3181 (40.5)	1782 (40.6)
Higher general	2295 (29.2)	1089 (24.8)
University	1399 (17.8)	594 (13.5)
Lifestyle factors		
Smoking status, n(%)		
Never	2474 (31.3)	817 (29.6)
Former	3771 (47.7)	1176 (42.6)
Current	1655 (20.9)	766 (27.8)
Physical activity, METh/wk	70.1 [40.3, 103.4]	67.2 [38.0, 99.6]
Cardiovascular risk factors		
BMI, kg/m^2	27.2 (4.2)	27.6 (4.5)
Overweight, n(%)	3657 (47.0)	1025 (46.0)
Obesity, n(%)	1634 (21.0)	539 (24.2)
Serum lipids, mmol/L		
Total cholesterol	5.74 (1.02)	5.64 (1.04)
HDL	1.41 (0.41)	1.38 (0.44)
Hypercholesterolemia, n(%)	2833 (37.4)	865 (37.7)
Fasting glucose, mmol/L	5.50 [5.10, 6.00]	5.50 [5.10, 6.10]
T2D, n(%)	917 (11.7)	379 (13.3)
SBP, mmHg	139.8 (21.2)	138.9 (21.4)
Hypertension, n(%)	4926 (62.8)	1606 (63.8)
CVD, n(%)	709 (9.6)	286 (7.2)
Medication use, n(%)[b]		
Antihypertensive drugs	2530 (33.3)	898 (31.5)
Kidney function		
eGFR, mL/min per 1.73 m^2	78.8 (14.9)	81.2 (15.3)
eGFR <60, n(%)	837 (10.6)	195 (8.9)
Kidney damage		
ACR, mg/g[c,d]	3.40 [2.19, 6.32][c]	3.74 [2.27, 6.95][d]
ACR >30, n(%)[c,d]	131 (5.2)[c]	69 (7.8)[d]

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^2. Obesity is defined as BMI >30 kg/m^2. Hypercholesterolemia is defined as total serum cholesterol ≥6.5 mmol/L and/or lipid reducing drug use. T2D is considered 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 ≥4h or ≥11.1 mmol/L if not fasted). Hypertension is present in case of SBP ≥mmHg or diastolic blood pressure ≥90 mmHg and/or blood pressure lowering drug use. CVD is defined as coronary heart disease and/or stroke. 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; ACR, albumin-to-creatinine ratio. [a] Missing data differ per variable; valid percentages are presented. [b] Coded according to the ATC classification system: antihypertensive drugs (C02, C03, C07, C09). [c] Based on n=2505 participants with both GFR and ACR data. [d] Based on n=1201 participants who were part of sub-cohort three.

Supplemental Table 3 Sensitivity analyses of associations of coffee consumption and longitudinal eGFR in 7914 participants of the Rotterdam Study.

			Total coffee consumption (cups/day)								
	Continuous		0		>0-2		>2-4		>4		P_{trend}
	β (95% CI)	N	β (95% CI)	N	β	N	β (95% CI)	N	β (95% CI)	N	
Main analysis model 3	0.04 (-0.10,0.18)	7914	0.93 (-0.61,2.47)	279	Ref	2026	-0.04 (-0.72,0.65)	3423	0.29 (-0.50,1.08)	2186	0.67
Excluding high coffee intake[a]	0.02 (-0.13,0.17)	7900	0.93 (-0.60,2.48)	279	Ref	2026	-0.03 (-0.71,0.65)	3423	0.27 (-0.52,1.06)	2172	0.70
Excluding high eGFR[b]	0.04 (-0.11,0.18)	7912	0.98 (-0.56,2.52)	279	Ref	2025	-0.01 (-0.69,0.67)	3423	0.29 (-0.50,1.08)	2185	0.66

Values are regression coefficients (β) and corresponding 95% confidence intervals (95% CI) from linear mixed models of the association between coffee consumption per one cup/day increase and in categories and longitudinal assessments of eGFR in mL/min per 1.73 m^2 during follow-up. Model 3: 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), systolic blood pressure (mmHg), total serum cholesterol (mmol/L), body mass index (kg/m^2) and blood pressure lowering drug use (2 categories). eGFR, estimated glomerular filtration rate; N, sample size; CI, confidence interval. [a] Defined as coffee consumption >14 cups/day. [b] Defined as eGFR >138 mL/min per 1.73 m^2.

Supplemental Table 4 Sensitivity analyses of associations of coffee consumption and longitudinal eGFR in 7914 participants of the Rotterdam Study, in the total cohort, and according to CKD risk factors.

	Sample size	Continuous β (95% CI)	P-value
Total cohort			
Main analysis model 3	7914	0.04 (-0.10,0.18)	0.55
Excluding non-coffee drinkers	7635	0.08 (-0.07,0.23)	0.30
Age (y)			
≤60			
Main analysis model 3	2460	-0.08 (-0.30,0.14)	
Excluding non-coffee drinkers	2299	-0.02 (-0.26,0.21)	0.85
>60-70			
Main analysis model 3	2927	-0.12 (-0.34,0.10)	
Excluding non-coffee drinkers	2857	-0.09 (-0.32,0.14)	0.45
>70			
Main analysis model 3	2527	0.84 (0.51,1.18)	
Excluding non-coffee drinkers	2479	0.91 (0.57,1.26)	0.00
Sex			
Men			
Main analysis model 3	3415	0.04 (-0.17,0.24)	
Excluding non-coffee drinkers	3318	0.09 (-0.13,0.30)	0.33
Women			
Main analysis model 3	4499	0.03 (-0.16,0.23)	
Excluding non-coffee drinkers	4317	0.05 (-0.16,0.26)	0.62
Smoking status			
Never			
Main analysis model 3	2478	-0.08 (-0.36,0.19)	
Excluding non-coffee drinkers	2345	-0.05 (-0.35,0.25)	0.74
Former			
Main analysis model 3	3778	0.17 (-0.03,0.39)	
Excluding non-coffee drinkers	3680	0.22 (-0.00,0.44)	0.05
Current			
Main analysis model 3	1658	-0.05 (-0.31,0.21)	
Excluding non-coffee drinkers	1610	-0.02 (-0.30,0.25)	0.88
Hypertension			
No			
Main analysis model 3	2964	0.08 (-0.12,0.28)	0.42
Excluding non-coffee drinkers	2835	0.11 (-0.11;0.32)	0.34
Yes			
Main analysis model 3	4950	0.04 (-0.15,0.24)	0.66
Excluding non-coffee drinkers	4800	0.09 (-0.11,0.29)	0.39
T2D			
No			
Main analysis model 3	6985	0.01 (-0.14,0.16)	0.92
Excluding non-coffee drinkers	6731	0.03 (-0.12,0.19)	0.67
Yes			
Main analysis model 3	929	0.42 (-0.05,0.88)	0.08
Excluding non-coffee drinkers	904	0.52 (0.03,1.00)	0.04

Supplemental Table 4 continued

	Sample size	Continuous β (95% CI)	P-value
CVD			
No			
Main analysis model 3	7164	0.04 (-0.10,0.19)	0.57
Excluding non-coffee drinkers	6906	0.08 (-0.07,0.23)	0.31
Yes			
Main analysis model 3	751	-0.04 (-0.59,0.52)	0.90
Excluding non-coffee drinkers	730	0.00 (-0.58,0.59)	0.99
Hypercholesterolemia			
No			
Main analysis model 3	4967	0.06 (-0.12,0.23)	0.51
Excluding non-coffee drinkers	4795	0.10 (-0.08,0.29)	0.28
Yes			
Main analysis model 3	2947	0.00 (-0.25,0.25)	1.00
Excluding non-coffee drinkers	2840	0.03 (-0.23,0.29)	0.82
BMI (kg/m^2)			
≤25			
Main analysis model 3	2535	-0.01 (-0.26,0.24)	0.92
Excluding non-coffee drinkers	2429	0.03 (-0.24,0.29)	0.84
>25-30			
Main analysis model 3	3718	-0.08 (-0.29,0.13)	0.44
Excluding non-coffee drinkers	3594	-0.07 (-0.29,0.15)	0.53
>30			
Main analysis model 3	1661	0.32 (0.01,0.63)	0.04
Excluding non-coffee drinkers	1612	0.40 (0.07,0.72)	0.02

Values are regression coefficients (β) and corresponding 95% confidence intervals (95% CI) from linear mixed models of the association between coffee consumption per one cup/day increase and longitudinal assessments of eGFR in mL/min per 1.73 m^2 during follow-up. Estimates are adjusted for age (years, except when stratified), sex (2 categories, except when stratified), socioeconomic status (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), tea consumption (cups/day), alcohol consumption (glasses/day), SBP (mmHg, except when stratified by hypertension), total serum cholesterol (mmol/L, except when stratified by hypercholesterolemia), BMI (kg/m^2, except when stratified), 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 ≥4h 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. eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; CI, confidence interval; T2D, type 2 diabetes; CVD, cardiovascular disease; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Supplemental Table 5 Baseline characteristics of 2505 participants with additional ACR data 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	2505	164	637	934	770
Coffee consumption, cups/day	3.25 [1.39, 5.11]	0.00 [0.00, 0.00]	1.39 [0.96, 1.39]	3.25 [3.25, 3.25]	5.11 [5.11, 6.96]
Sociodemographic factors					
Age, y	57.0 (6.4)	55.7 (6.7)	58.8 (7.3)	56.8 (6.4)	55.8 (5.1)
Sex, n(%)					
Men	1052 (42.0)	53 (32.3)	214 (33.6)	358 (38.3)	427 (55.5)
Women	1453 (58.0)	111 (67.7)	423 (66.4)	576 (61.7)	343 (44.5)
Education, n(%)					
Primary	245 (9.8)	15 (9.1)	79 (12.4)	83 (8.9)	68 (8.8)
Intermediate	864 (34.5)	52 (31.7)	247 (38.8)	334 (35.8)	231 (30.0)
Higher general	684 (27.3)	54 (32.9)	159 (25.0)	244 (26.1)	227 (29.5)
University	705 (28.1)	43 (26.2)	151 (23.7)	268 (28.7)	243 (31.6)
Lifestyle factors					
Smoking status, n(%)					
Never	784 (31.3)	81 (49.4)	244 (38.3)	294 (31.5)	165 (21.4)
Former	1120 (44.7)	51 (31.1)	291 (45.7)	450 (48.2)	328 (42.6)
Current	595 (23.8)	32 (19.5)	101 (15.9)	187 (20.0)	275 (35.7)
Physical activity, METh/wk	42.4 [18.0, 82.1]	43.4 [15.4, 82.7]	50.9 [19.6, 81.9]	43.6 [20.5, 83.5]	34.1 [15.0, 80.1]
Cardiovascular risk factors					
BMI, kg/m^2	27.5 (4.5)	26.7 (5.2)	27.6 (4.5)	27.5 (4.3)	27.7 (4.6)
Overweight, n(%)	1142 (45.6)	65 (39.6)	286 (44.9)	434 (46.5)	357 (46.4)
Obesity, n(%)	576 (23.0)	30 (18.3)	152 (23.9)	211 (22.6)	183 (23.8)
Serum lipids, mmol/L					
Total cholesterol	5.57 (1.06)	5.52 (1.10)	5.55 (1.11)	5.58 (1.04)	5.58 (1.05)
HDL	1.45 (0.43)	1.47 (0.42)	1.46 (0.46)	1.47 (0.42)	1.40 (0.42)
Hypercholesterolemia, n(%)	962 (38.4)	63 (38.4)	266 (41.8)	348 (37.3)	285 (37.0)
Fasting glucose, mmol/L	5.30 [4.90, 5.70]	5.20 [4.90, 5.60]	5.30 [4.90, 5.80]	5.30 [4.90, 5.62]	5.30 [5.00, 5.70]
T2D, n(%)	218 (8.7)	13 (7.9)	71 (11.1)	70 (7.5)	64 (8.3)
SBP, mmHg	132.6 (19.07)	128.8 (18.19)	133.7 (19.81)	132.7 (18.92)	132.4 (18.73)
Hypertension, n(%)	1252 (50.0)	73 (44.5)	357 (56.0)	473 (50.6)	349 (45.3)
CVD, n (%)	104 (4.2)	7 (4.3)	28 (4.4)	35 (3.7)	34 (4.4)

Supplemental Table 5 continued

	Total cohort	Coffee consumption (cups/day)			
		0 (non-consumers)	>0-2 (low intake)	>2-4 (moderate intake)	>4 (heavy intake)
Medication use, n(%)[a]					
Antihypertensive drugs	643 (25.7)	45 (27.4)	201 (31.6)	223 (23.9)	174 (22.6)
Kidney damage					
ACR, mg/g	3.40 [2.19, 6.32]	3.25 [2.25, 5.68]	3.54 [2.29, 6.70]	3.43 [2.19, 6.27]	3.35 [2.15, 6.18]
ACR >30, n(%)	131 (5.2)	11 (6.7)	37 (5.8)	44 (4.7)	39 (5.1)

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^2. Obesity is defined as BMI >30 kg/m^2. 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 ≥4h 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. ACR, albumin-to-creatinine ratio; N, sample size; MET, metabolic equivalent task; BMI, body mass index; HDL, high-density lipoprotein cholesterol; T2D, type 2 diabetes; SBP, systolic blood pressure; CVD, cardiovascular disease. [a] Coded according to the ATC classification system: antihypertensive drugs (C02, C03, C07, C09).

Supplemental Table 6 Multivariable adjusted associations between coffee consumption and longitudinal urinary ACR[a] in 2505 participants of the Rotterdam Study.

			Total coffee consumption (cups/day)				
	Continuous		0 (n=164)	>0-2 (n=637)	>2-4 (n=934)	>4 (n=770)	P_{trend}
	β (95% CI)	P-value	β (95% CI)	β	β (95% CI)	β (95% CI)	
Model 1	0.01 (-0.01,0.03)	0.17	-0.03 (-0.17,0.11)	Ref	-0.01 (-0.09,0.07)	0.06 (-0.03,0.14)	0.25
Model 2	0.00 (-0.01,0.02)	0.74	-0.02 (-0.16,0.12)	Ref	-0.02 (-0.10,0.06)	0.02 (-0.07,0.11)	0.81
Model 3	0.01 (-0.01,0.02)	0.49	-0.01 (-0.15,0.13)	Ref	-0.01 (-0.09,0.08)	0.04 (-0.05,0.12)	0.50

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 with longitudinal measures of urinary ACR in mg/g during follow-up. Model 1: adjusted for age (years), sex (2 categories), and socioeconomic status (4 categories). ACR, albumin-to-creatinine ratio; CI, confidence interval. Model 2: 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: additionally adjusted for systolic blood pressure (mmHg), total serum cholesterol (mmol/L), body mass index (kg/m^2), and blood pressure lowering drug use (2 categories). [a]Natural logarithm-transformed

Supplemental Table 7 Multivariable adjusted associations between coffee consumption and incident reduced kidney function in 4649 participants of the Rotterdam Study.

			Total coffee consumption (cups/day)				
	Continuous		0 (n=192)	>0-2 (n=1029)	>2-4 (n=1996)	>4 (n=1432)	P_{trend}
	HR (95% CI)	P value	HR (95% CI)	HR	HR (95% CI)	HR (95% CI)	
Cases			17	157	286	159	
Model 1	0.97 (0.93,1.01)	0.16	1.02 (0.62,1.69)	Ref	0.82 (0.67,1.00)	0.84 (0.67,1.06)	0.07
Model 2	0.96 (0.92,1.01)	0.11	0.96 (0.58,1.61)	Ref	0.81 (0.66,0.98)	0.82 (0.65,1.03)	0.04
Model 3	0.97 (0.93,1.01)	0.16	0.92 (0.55,1.53)	Ref	0.81 (0.67,0.99)	0.84 (0.66,1.06)	0.07

Values are HRs and corresponding 95% confidence intervals (95% CI) from Cox proportional hazards models of the association between coffee consumption per cup/day increase and in categories with risk of incident reduced kidney function. Reduced kidney function is defined as single assessment of eGFR <60 mL/min per 1.73 m^2. HR, hazard ratio; CI, confidence interval. Model 1: adjusted for age (years), sex (2 categories), socioeconomic status (4 categories), and sub-cohort (3 categories). Model 2: additionally adjusted for smoking status (3 categories), physical activity (MET hours/week), diet quality (score), energy intake (kcal/day), alcohol consumption (glasses/day), tea consumption (cups/day). Model 3: additionally adjusted for systolic blood pressure (mmHg), total serum cholesterol (mmol/L), body mass index (kg/m^2), and blood pressure lowering drug use (2 categories).

Chapter 5

Coffee consumption and risk of kidney function decline in a Dutch population-based cohort

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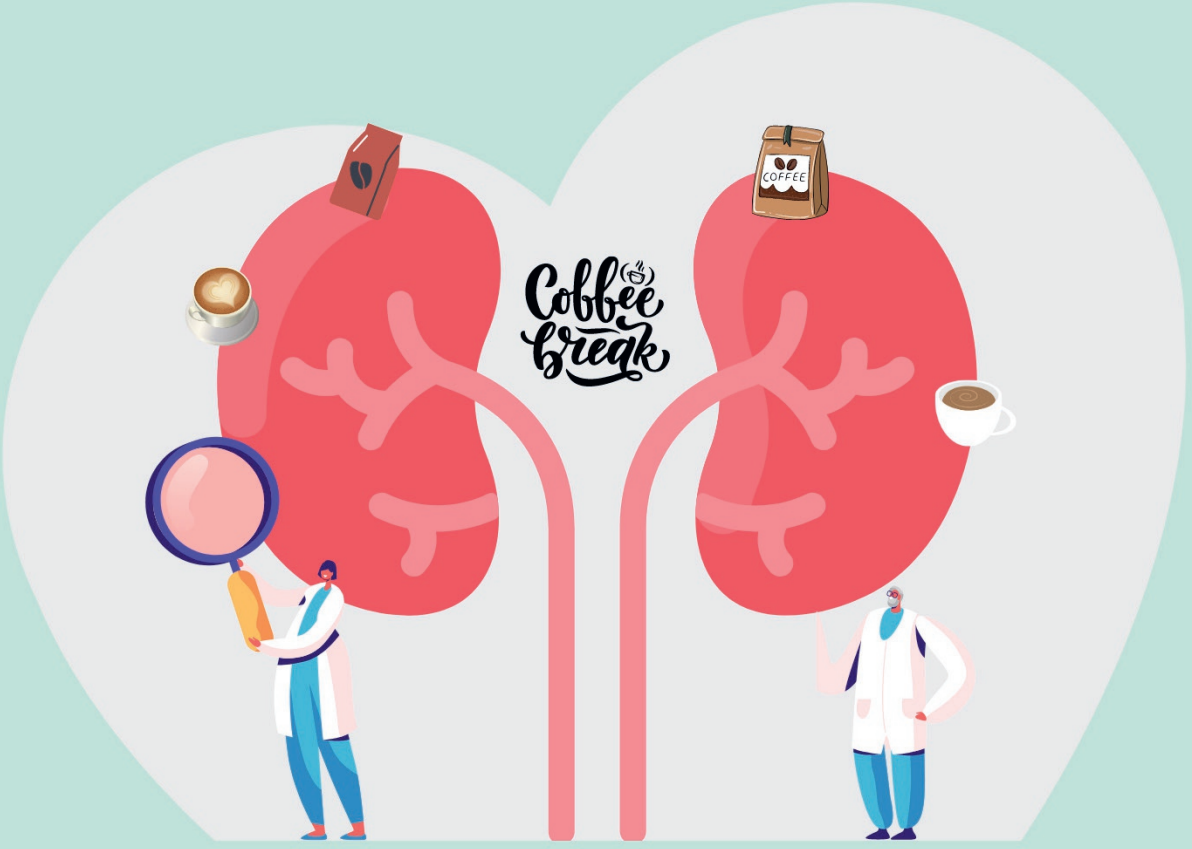
Under review



Abstract

Background and aims Association of coffee consumption with estimated glomerular filtration rate (eGFR) change in the general population is inconclusive. We investigated associations of coffee consumption with annual eGFR change and incident chronic kidney disease (CKD) in a large Dutch population-based study.

Methods and results This study was performed in 78,346 participants free of CKD in the population-based Lifelines Cohort Study. Coffee consumption was assessed at baseline using food frequency questionnaires. Outcomes were annual eGFR change and a composite kidney outcome (defined as eGFR <60 mL/min per 1.73 m^2 or >20% eGFR decline). Multivariable linear and logistic regression analyses were used to evaluate the associations of coffee consumption (categories and cups/day) with kidney outcomes. Overall, 90% of the participants drank coffee daily and 36% drank >2-4 cups/day. Unadjusted mean ± SD annual eGFR change ranged from -2.86 ± 2.96 (for non-coffee drinkers) to -2.35 ± 2.62 (for participants consuming >6 cups/day) mL/min per 1.73 m^2. During 3.6 ± 0.9 years of follow-up, 11.1% of participants reached the composite kidney outcome. As compared to non-coffee drinkers, higher coffee consumption was associated with less annual eGFR decline in multivariable models (β [95% CIs] ranged from 0.15 [0.07, 0.22] for >0-2 cups/day to 0.29 [0.20, 0.38] for >6 cups/day, P-trend <0.001). Consumption of one more cup of coffee per day was associated with a 3% lower risk of the composite kidney outcome (OR [95%CI], 0.97 [0.96, 0.99]).

Conclusion Coffee consumption was inversely associated with annual eGFR change and the composite kidney outcome in a dose-response manner in this large prospective population-based cohort.

Introduction

Chronic kidney disease (CKD) is an increasing global public health problem that leads to high rates of morbidity and premature mortality (1, 2). CKD imposes a large burden on health and social care system, especially considering the high cost of kidney replacement therapy (dialysis and transplantation) (3). Lifestyle modification, including dietary changes, may importantly contribute to the prevention of CKD, and its potential complications (4-6).

Coffee is one of the most consumed beverages in the world and contains numerous substances (i.e., caffeine, chlorogenic acids, diterpenes, cafestol, trigonellin, kahweol, magnesium, and potassium) that may have antioxidant, anti-inflammatory, antifibrotic and anticancer effects, and may improve gut microbiome and liver health (7-9). Observational studies and meta-analyses have reported that coffee consumption has more often been associated with a lower risk of various outcomes (10, 11), including all-cause mortality (12), type 2 diabetes (13), hypertension (14), cardiovascular disease (15), liver and gastrointestinal diseases (16), neurological disorders (17), and certain types of cancer(18). Coffee consumption has been associated with a lower risk of incident CKD among 14,209 US middle-aged adults (19). This finding has been replicated by one study (20) but not by other studies (21-23). A recent meta-analysis of 12 studies involving 505,842 participants has demonstrated significant inverse associations of coffee consumption with incident CKD, end-stage kidney disease (ESKD), and albuminuria, but no results were provided on estimated glomerular filtration rate (eGFR) change (24). The association between coffee consumption and annual changes in eGFR is also inconclusive (20, 25). Apart from the relatively small sample sizes of most of previous studies, little is known on the long-term association between coffee consumption and eGFR change, and a potential dose-response relationship. Therefore, the purpose of the present study was to investigate a potential dose-response association of coffee consumption with annual change in eGFR and a composite kidney outcome (incident CKD or a >20% eGFR decline) in a large population-based prospective cohort in the Netherlands.

Methods

Study population

Lifelines is a multi-disciplinary prospective population-based cohort study in a unique three-generation design examining the health and health-related behaviours of 167,729 participants living in the Northern Netherlands. It employs a broad range of investigative procedures in assessing the biomedical, sociodemographic, behavioural, physical and psychological factors which contribute to the health and disease of the general population, with a special focus on multi-morbidity and complex genetics (26). The Lifelines study population is generally representative for the adult population in the Northern Netherlands (27). Participants were

enrolled from 2006 to 2011 through invitation by their general practitioners. All participants were invited to the first follow-up assessment from 2014 to 2019. All participants provided informed consent when they entered the cohort. The Lifelines Cohort Study is conducted according to the principles of the Declaration of Helsinki and is approved by the medical ethical review committee of the University Medical Centre Groningen.

Among 152,728 adult participants at baseline, 1840 died and another 50,240 participants had no follow-up data available, yielding 100,648 participants who took part in the first follow-up round. Participants with CKD (defined as having an eGFR <60 mL/min per 1.73 m^2) (28) at baseline were excluded (n=1916) and those with no baseline dietary intake information (n=2064) or with no serum creatinine information (n=7436) were excluded. We evaluated potential errors in dietary reporting based on the Schofield equation: the ratio between energy intake (EI) and basal metabolic rate (BMR), and applied the Goldberg cut-off (29, 30). Briefly, EI/BMR values <0.5 and >2.75 were considered implausible and represented an additional exclusion criterion. We excluded 10,886 participants with implausible energy intake, yielding 78,346 participants (45,751 females and 32,595 males) for the current study (**Supplemental Fig. 1**).

Assessment of coffee and other dietary factors

In the Lifelines Cohort Study, coffee consumption and other dietary factors were evaluated by a self-administered 110-item food frequency questionnaire (FFQ) at baseline (26, 31). This FFQ included questions on the frequency and portion size of food items during the last month. Participants were asked to report their frequency of coffee consumption per week or per month and the average number of cups (1 cup was defined as 125 gram). Any type of coffee (instant, ground, decaffeinated, and caffeinated coffee) was included. Caffeinated vs decaffeinated coffee and filtered vs unfiltered coffee were not distinguished in the questionnaire. Alcohol intake was categorised as no (ethanol intake of 0 g/d), light (0-5g/d for women and 0-10 g/d for men), moderate (>5-10 g/d for women and >10-20 g/d for men), and heavy (≥10 g/d for women and ≥20 g/d for men). Overall diet quality was assessed by the Lifelines Diet Score (LLDS). Detailed information on the LLDS has been described elsewhere (32, 33). In short, the LLDS ranks consumption of nine healthy food groups (vegetables, fruit, whole grain products, legumes and nuts, fish, oils and soft margarines, unsweetened dairy, coffee, and tea) and three unhealthy food groups (red and processed meat, butter and hard margarines, and sugar-sweetened beverages). Daily intake for each healthy and unhealthy food group (in gram/1000 kcal) was categorised into quintiles, awarding 0 to 4 points (negative groups scored inversely). The LLDS was obtained by the sum of 12 component scores, ranging from 0 to 48, with higher scores reflecting better diet quality. Then, the LLDS was divided into tertiles (low, middle, and high diet quality).

Assessment of other covariates

Sociodemographic characteristics and lifestyle factors were based on the self-administered questionnaires. Education level was categorised as low (never been to school or elementary school only or lower vocational or secondary school), middle (intermediate vocational school or intermediate/higher secondary school), and high (higher vocational school or university). Smoking was classified as current smoker, former smoker, and non-smoker. The validated Short Questionnaire to ASsess Health-enhancing physical activity (SQUASH) was used to evaluate time spent on non-occupational moderate to vigorous physical activity (minutes/week). Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2). Blood and urine laboratory assessments have been published previously in detail (26). Serum creatinine was measured by an enzymatic method traceable to isotope dilution mass spectrometry on a Roche Modular analyser (Roche Diagnostics, Mannheim, Germany). Blood pressure was measured 10 times during 10 min with Dinamap, PRO 100V2 and hypertension was defined as systolic blood pressure ≥140 or diastolic blood pressure ≥ 90 mmHg or the use of antihypertensive medication. Participants were considered as having diabetes if they had self-reported diabetes and/or a non-fasting plasma glucose ≥11.1 mmol/L and/or a measured glycated hemoglobin (HbA1c) ≥6.5% and/or use of oral anti-diabetics and/or insulin. Prevalent cardiovascular disease (CVD) included coronary artery disease, heart failure, and/or stroke based on the self-reported questionnaires.

Assessment of kidney outcomes

The primary outcome of this study was the annual change in eGFR, calculated by subtracting eGFR at baseline from eGFR at the second visit and dividing by the participant-specific follow-up time in years. Estimated GFR was calculated based on serum creatinine using the 2012 Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI) (28). The secondary outcome was a composite kidney outcome including a >20% eGFR decline or incident CKD, defined as a *de novo* occurrence of an eGFR <60 mL/min per 1.73 m^2 at the first follow-up visit compared to baseline visit.

Statistical analysis

Total coffee consumption was categorised into five groups: 0 cup, >0-2 cups, >2-4 cups, >4-6 cups, or >6 cups per day. Baseline characteristics of the Lifelines Cohort were obtained in predefined categories of coffee consumption. Data are presented as mean ± standard deviation (SD), median (interquartile range), or percentage, as appropriate.

Multivariable linear regression was used to analyse the association between coffee consumption (five categories or continuous per cup increment) and annual change in eGFR. Positive betas represent less eGFR decline, and negative betas represent more eGFR decline. Odds ratios (95% confidence intervals) for the association between coffee consumption and composite kidney outcome were calculated by means of logistic regression analysis. Model 1

was adjusted for age and sex. Model 2 was further adjusted for education level (low, middle and high), physical activity, smoking (current, former, and non-smokers), alcohol intake (no, light, moderate, and heavy), total energy intake, and intake of sugar-sweetened beverages, red and processed meat, dairy products, fruits and vegetables, and tea. Finally, we additionally adjusted for baseline eGFR, systolic BP, and BMI (Model 3).

To understand possible dose-response associations between coffee consumption and kidney outcomes, we performed restricted cubic splines by multivariable ordinary least squares and multivariable logistic regression with three knots located at the10th, 50th, 90th percentile of coffee consumption using non-coffee consumers as the reference (34). Subsequently, subgroup analyses were conducted to understand potential effect modification by specific baseline variables. We stratified the participants by age (younger adults under 45 years and older adults over 45 years), sex (male and female), education level (low, middle and high education), smoking (current, former and non-smoker), diet quality (low, middle ,and high diet quality), BMI categories (18.5-25, >25-30, and >30 kg/m^2), diabetes (yes and no), hypertension (yes and no), cardiovascular disease (yes and no), or gastrointestinal disease (yes and no). Potential effect modification was assessed by comparison of estimates with 95% CIs across subgroups. Significant effect modification was present if 95% CIs of two groups failed to overlap. If 95% CI of one group contains the point estimate of the other group, effect modification was not present (35). Sensitivity analyses were performed using a secondary composite kidney outcome (incident CKD or a >30% eGFR decline). We further repeated the analysis after excluding non-coffee drinkers. A two-tailed P value < 0.05 was considered statistically significant. All statistical analyses were conducted using R version 3.4.2 (Vienna, Austria).

Results

Baseline characteristics

Mean age of the population was 46 ± 13 years, and 58% were female. Of total participants, 90% were daily coffee drinkers and 36% of the participants drank >2-4 cups per day. Baseline characteristics according to categories of coffee consumption are presented in **Table 1**. Compared to coffee drinkers, non-coffee drinkers were younger, more often female, highly educated, non-smoker, non-alcohol drinker, and tea drinker. Among coffee drinkers, participants with higher daily coffee intake were more often male, older, lower educated, and current smoker. They were less physically active and had higher BMI, higher alcohol intake, and lower tea intake. They had a higher prevalence of diabetes, cardiovascular disease and lower proportion of gastrointestinal disease at baseline.

Table 1 Characteristics by daily coffee consumption among 78,346 participants free of CKD at baseline in the Lifelines Cohort.

		Coffee consumption (cups/day)				
	Total	**0**	**>0-2**	**>2-4**	**>4-6**	**>6**
Participants, n	78,346	7816	15,945	28,396	18,474	7715
Sociodemographic factor						
Age, years	45.8±12.6	35.7±11.7	42.8±14.0	48.5±12.2	48.3±10.7	47.1±9.6
Sex, % female	58.4	78.3	67.9	60.7	44.2	33.6
Education (%)						
Low	28.7	18.9	26.5	30.3	30.8	31.9
Middle	39.9	46.0	40.8	38.2	39.3	39.7
High	31.0	34.8	32.3	31.1	29.4	27.8
Lifestyle factors						
Physical activity (min/week)	195 (70, 375)	200 (80, 375)	210 (90, 390)	210 (90, 390)	180 (60, 360)	150 (30, 360)
Smoking (%)						
No	47.3	70.9	58.9	46.7	36.8	27.3
Former	36.1	17.6	29.5	39.9	42.5	39.3
Current	16.6	11.6	11.7	13.4	20.7	33.4
Alcohol intake, g/day	4.0 (0.9, 10.4)	1.2 (0.1, 4.1)	2.7 (0.7, 7.6)	5.2 (1.3, 10.5)	6.4 (1.7, 12.5)	6.7 (1.7,15.8)
No	2.4	5.8	2.8	1.8	1.6	2.2
Light	71.2	83.5	77.7	71.5	65.1	58.7
Moderate	19.3	8.0	14.1	20.2	24.6	25.6
Heavy	7.1	2.7	5.4	6.4	8.7	13.6
Dietary factors						
Total energy intake, kcal/day	2076±607	1959±573	1962±583	2039±569	2171±616	2336±685
Sugar-sweetened beverages, g/day	91 (21, 197)	120 (33,279)	100 (27, 213)	77 (21, 179)	83 (21, 188))	92 (21, 201)
Red and processed meat, g/day	66 (46, 87)	63 (42, 83)	61 (39, 82)	64 (45, 85)	69 (51, 90)	76 (56, 97)
Dairy products, g/day	279 (174, 406)	242 (144, 369)	261 (162, 389)	289 (186, 413)	291 (186, 420)	273 (171, 410)
Fruits and vegetables, g/day	224 (149, 327)	200 (126, 312)	220 (146, 327)	236 (150, 331)	226 (150, 327)	193 (121, 300)
Tea intake, g/day	232 (45, 348)	465 (232, 697)	232 (116, 465)	232 (80, 348)	116 (22, 232)	36 (0, 161)
Diet quality (%)						
Low	34.9	48.0	40.6	31.1	29.9	35.5
Middle	31.2	30.2	30.5	30.5	32.2	34.1
High	33.9	21.8	28.9	38.5	37.9	30.4

Table 1 continued

	Total	Coffee consumption (cups/day)				
		0	>0-2	>2-4	>4-6	>6
Clinical factors						
eGFR (mL/min per 1.73 m^2)	95.9±14.3	103.5±14.6	97.9±15.1	93.8±13.9	94.2±13.3	96.0±12.8
Serum creatinine (mmol/L)	74.9±12.1	69.5±11.0	72.2±11.8	73.5±12.2	74.7±12.5	75.9±12.4
Systolic BP, mm Hg	125.7±16.9	119.6±13.5	124.2±15.4	126.6±15.6	127.2±14.8	128.1±14.2
Diastolic BP, mm Hg	73.9±10.3	70.5±8.4	72.8±9.3	74.2±9.2	75.1±9.1	75.9±9.3
BMI, kg/m^2	26.0±4.2	25.4±4.8	25.5±4.3	26.0±4.0	26.4±3.9	26.8±4.0
Cholesterol (mmol/L)	5.1±1.0	4.7±0.9	5.0±1.0	5.2±1.0	5.2±1.0	5.3±1.0
Triglycerides (mmol/L)	1.2±0.8	1.0±0.7	1.1±0.7	1.2±0.8	1.2±0.8	1.3±1.0
HbA1c (%)	5.6±0.4	5.5±0.4	5.5±0.4	5.6±0.4	5.6±0.5	5.6±0.5
Diabetes (%)	3.1	1.7	2.9	3.2	3.5	3.7
Hypertension (%)	22.0	14.4	21.1	24.5	22.7	21.0
Cardiovascular disease (%)	2.6	1.0	2.3	2.9	2.9	3.2
Gastrointestinal disease (%)	12.2	15.5	13.7	11.8	11.0	10.3

Data are presented as mean ± standard deviation, median (interquartile range) or percentage, as appropriate. P value for all the variables: <0.001. Definitions: education level: low, never been to school or elementary school only or lower vocational or secondary schooling; intermediate, intermediate vocational schooling or intermediate/higher secondary schooling; higher, higher vocational schooling or university. Alcohol intake: no, ethanol intake of 0 g/d; light, 0-5g/d for women and 0-10 g/d for men; moderate, >5-10 g/d for women and >10-20 g/d for men; heavy, ≥10 g/d for women and ≥20 g/d for men. Diet quality: high LLDS score <22; middle, LLDS 22-26; low, LLDS>26. CKD, chronic kidney disease; BMI, body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate; LLDS, Lifelines Diet Score.

Coffee consumption and annual change in eGFR

During a mean ± SD follow-up time of 3.6 ± 0.9 years, the mean ± SD annual eGFR change was -2.48 ± 2.72 mL/min per 1.73 m^2. The distribution of annual change in eGFR is shown in **Supplemental Fig. 2.** Associations between coffee consumption categories relative to non-coffee drinkers and annual eGFR change are shown in **Table 2**. Coffee drinkers had less annual eGFR decline as compared to non-coffee drinkers (β [95%CI], 0.15 [0.07, 0.22] mL/min per 1.73 m^2 for >0-2 cups per day, 0.19 [0.11, 0.26] mL/min per 1.73 m^2 for >2-4 cups per day, 0.24 [0.16, 0.32] mL/min per 1.73 m^2 for >4-6 cups, and 0.29 [0.20, 0.38] mL/min per 1.73 m^2 for >6 cups per day, P-trend <0.001) after adjustment for potential confounders. Every one cup/day increment of coffee consumption was associated with 0.03 mL/min per 1.73 m^2 less annual eGFR decline during follow-up (β [95%CI], 0.03 [0.02, 0.04], P<0.001). We observed a dose-response association between coffee consumption and annual change in eGFR (P <0.001) (**Fig. 1**). This association was also observed among coffee drinkers only (**Supplemental Table 1)**.

The associations between per cup increment of coffee consumption and annual change in eGFR stratified by baseline variables are shown in **Fig. 2**. Based on the comparison of estimates with 95% CIs across subgroups, potential effect modification was observed for education level and diabetes. The association between coffee consumption and annual eGFR change seemed to be stronger among low-educated participants than among higher educated participants. The associations appeared to be stronger in individuals with diabetes compared to those without diabetes. Associations were similar in strata of age, sex, smoking, diet quality, BMI categories, hypertension, cardiovascular disease, and gastrointestinal disease.

Table 2 Association between daily coffee consumption and annual change in eGFR during follow-up among 78,346 participants free of CKD at baseline in the Lifelines Cohort.

	Coffee consumption (cups/day) β (95% CI)						Per cup increment of coffee consumption	
	0	>0-2	>2-4	>4-6	>6	P_{trend}	β (95% CI)	P-value
Annual change in eGFR (mean ± SD), mL/min per 1.73 m^2 #	-2.86±2.96	-2.51±2.78	-2.40±2.63	-2.40±2.60	-2.35±2.62	<0.001		
Model 1	Reference	0.19 (0.11, 0.26)	0.24 (0.17, 0.31)	0.30 (0.22, 0.37)	0.31 (0.22, 0.40)	<0.001	0.03 (0.02, 0.04)	<0.001
Model 2	Reference	0.20 (0.13, 0.28)	0.26 (0.19, 0.34)	0.33 (0.25, 0.41)	0.36 (0.26, 0.46)	<0.001	0.04 (0.03, 0.05)	<0.001
Model 3	Reference	0.15 (0.07, 0.22)	0.19 (0.11, 0.26)	0.24 (0.16, 0.32)	0.29 (0.20, 0.38)	<0.001	0.03 (0.02, 0.04)	<0.001

Model 1. Adjusted for age and sex. Model 2. Model 1 plus education level, physical activity, smoking, alcohol intake, total energy intake, intake of sugar-sweetened beverages, red and processed meat, dairy products, fruits and vegetables, and tea intake. Model 3. Model 2 plus baseline eGFR, systolic BP, and BMI. **#** Mean value of annual change in eGFR based on the categories of coffee consumption without adjustment. eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; CI, confidence interval; SD, standard deviation; BP, blood pressure; BMI, body mass index.

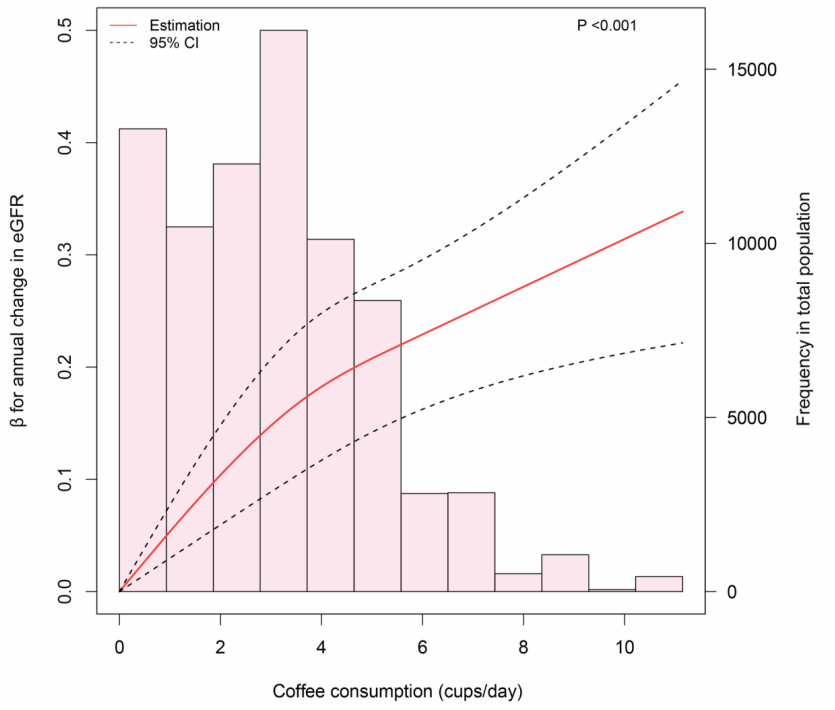


Fig. 1 Prospective association between coffee consumption (cups/day) and annual change in eGFR among 78,346 participants free of CKD at baseline in the Lifelines Cohort. Data were fit by multivariable ordinary least squares with 3-knot restricted cubic spline using non-coffee consumers as the reference. Overall association between coffee consumption and annual change in eGFR: P<0.001. The model was adjusted for age, sex, education level, physical activity, smoking, alcohol intake, total energy intake, intake of sugar-sweetened beverages, red and processed meat, dairy products, fruits and vegetables, tea intake, baseline eGFR, systolic BP, and BMI. eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; CI, confidence interval; BP, blood pressure; BMI, body mass index.

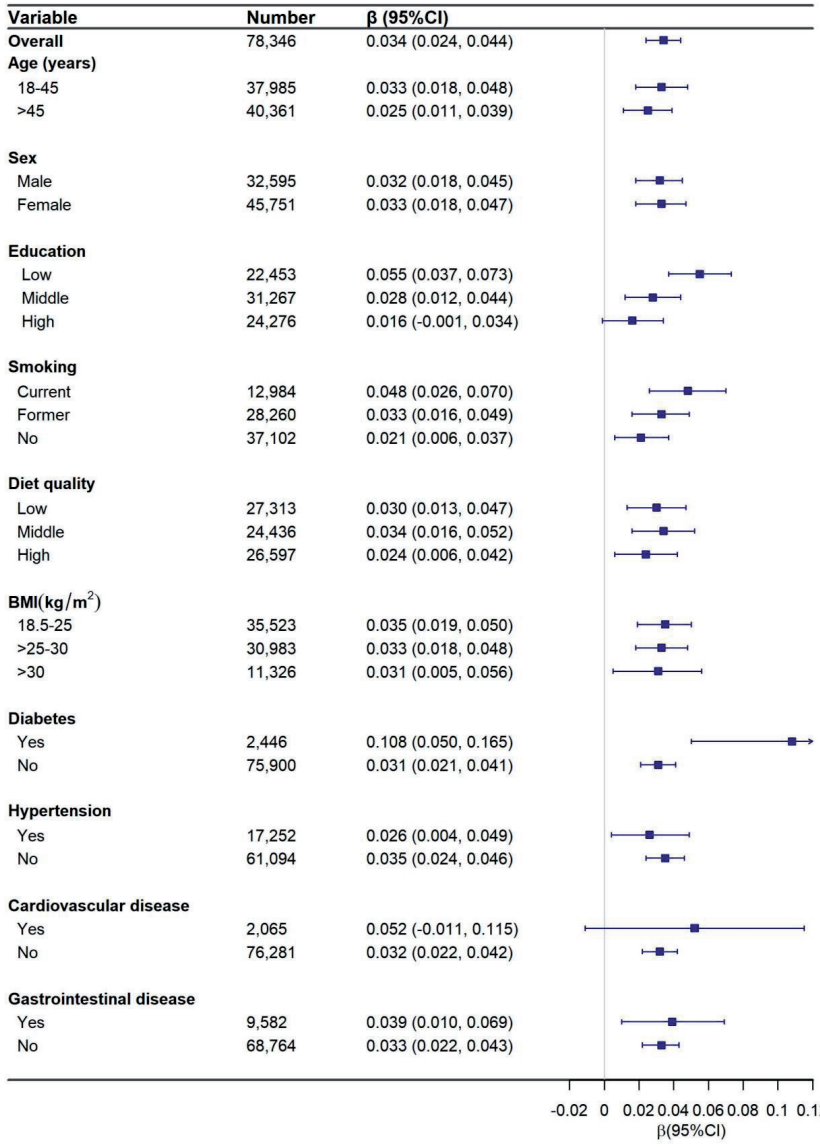


Fig. 2 Subgroup analyses of the association between daily coffee consumption and annual change in eGFR among 78,346 participants free of CKD at baseline in the Lifelines Cohort. Regression coefficient (β) represents the change in annual change in eGFR per cup increment of coffee consumption. Linear regression model adjusted for age, sex, education level, physical activity, smoking, alcohol intake, total energy intake, intake of sugar-sweetened beverages, red and processed meat, dairy products, fruits and vegetables, tea intake, baseline eGFR, systolic BP, and BMI (but not adjusted when stratified). eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; CI, confidence interval; BP, blood pressure; BMI, body mass index.

Coffee consumption and composite kidney outcome

During 3.6 ± 0.9 years of follow-up, 8735 (11.1%) participants reached the composite kidney outcome. Coffee drinkers had a lower risk of composite kidney outcome compared to non-coffee drinkers (OR [95%CI], 0.91 [0.83, 0.99] for >0-2 cup per day, 0.85 [0.78, 0.93] for >2-4 cups per day, 0.81 [0.74, 0.89] for >4-6 cups per day, 0.83 [0.74, 0.93] for >6 cups per day, P-trend <0.001) after multivariable adjustment (**Table 3**). Every one cup/day increment of coffee consumption was associated with a lower risk of the composite kidney outcome (OR [95%CI], 0.97 [0.96, 0.99], P<0.001). We observed a dose-response association between coffee consumption and the composite kidney outcome (P <0.001) (**Fig. 3**). The same association was observed among coffee drinkers only (**Supplemental Table 2)**. Our results were robust in a secondary composite kidney outcome (incident CKD or >30% eGFR decline, **Supplemental Table 3**) and a dose-response association was also observed (P <0.001) (**Supplemental Fig. 2**).

The association between coffee consumption and risk of composite kidney outcome was stronger among patients with diabetes, and was similar in subgroups of age, sex, education, smoking, diet quality, BMI categories, hypertension, cardiovascular disease, and gastrointestinal disease (**Fig. 4**).

Table 3 Association between daily coffee consumption and risk of composite kidney outcome (incident CKD or eGFR decline>20%) during follow-up among 78,346 participants free of CKD at baseline in the Lifelines Cohort.

	Coffee consumption (cups/day) OR (95% CI)						Per cup increment of coffee consumption	
	0	>0-2	>2-4	>4-6	>6	P_{trend}	OR (95% CI)	P-value
Events/Number	856/7816	1809/15,945	3295/28,396	1983/18,474	792/7715	0.029		
Model 1	Reference	0.94 (0.86, 1.02)	0.89 (0.82, 0.97)	0.85 (0.78, 0.93)	0.87 (0.78, 0.97)	<0.001	0.98 (0.97, 0.99)	<0.001
Model 2	Reference	0.92 (0.84, 1.01)	0.87 (0.79, 0.95)	0.83 (0.75, 0.91)	0.84 (0.75, 0.95)	<0.001	0.98 (0.96, 0.99)	<0.001
Model 3	Reference	0.91 (0.83, 0.99)	0.85 (0.78, 0.93)	0.81 (0.74, 0.89)	0.83 (0.74, 0.93)	<0.001	0.97 (0.96, 0.99)	<0.001

Model 1. Adjusted for age and sex. Model 2. Model 1 plus education level, physical activity, smoking, alcohol intake, total energy intake, intake of sugar-sweetened beverages, red and processed meat, dairy products, fruits and vegetables, and tea. Model 3. Model 2 plus baseline eGFR, systolic BP, and BMI. eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; CI, confidence interval; BP, blood pressure; BMI, body mass index.

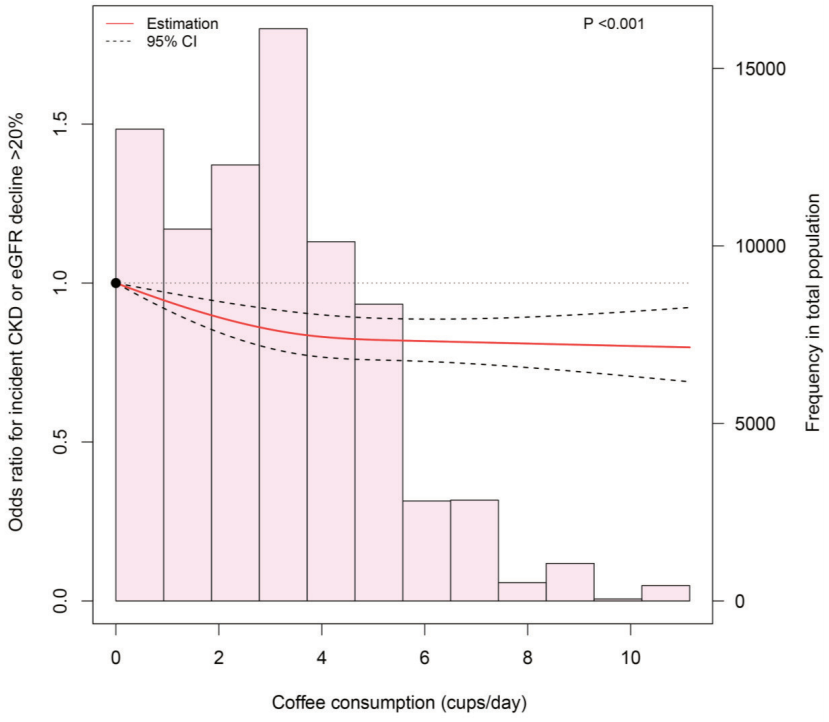


Fig. 3 Prospective association between coffee consumption (cups/day) and composite kidney outcome among 78,346 participants free of CKD at baseline in the Lifelines Cohort. Data were fit by multivariable logistic regression with 3-knot restricted cubic spline using non-coffee consumers as the reference (odds ratio=1). Overall association between coffee consumption and the composite kidney outcome (incident CKD or eGFR decline >20%): P<0.001. The model was adjusted for age, sex, education level, physical activity, smoking, alcohol intake, total energy intake, intake of sugar-sweetened beverages, red and processed meat, dairy products, fruits and vegetables, tea intake, baseline eGFR, systolic BP, and BMI. eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; CI, confidence interval; BP, blood pressure; BMI, body mass index.

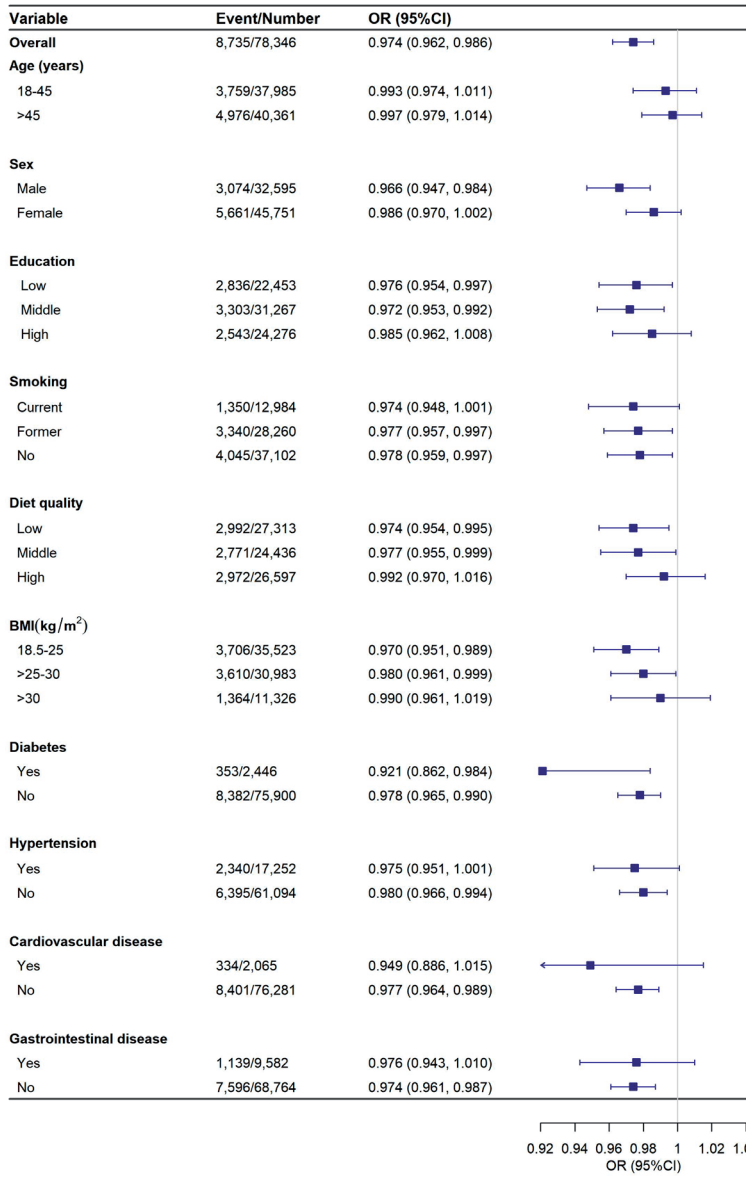


Fig. 4 Subgroup analyses of the association between daily coffee consumption and composite kidney outcome among 78,346 participants free of CKD at baseline in the Lifelines Cohort. Odds ratio (OR) for participants who experienced composite kidney outcome (incident CKD or eGFR decline >20%) with per cup increment of coffee consumption. Multivariable logistic regression model adjusted for age, sex, education level, physical activity, smoking, alcohol intake, total energy intake, intake of sugar-sweetened beverages, red and processed meat, dairy products, fruits and vegetables, tea, baseline eGFR, systolic BP, and BMI (but not adjusted when stratified). eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; CI, confidence interval; BP, blood pressure; BMI, body mass index.

Discussion

In this large general population-based cohort, we observed inverse associations between coffee consumption and annual eGFR decline and a composite kidney outcome of incident CKD or >20% eGFR decline after adjustment for potential confounders. Every one cup/day increment of coffee consumption was associated with 0.03 mL/min per 1.73 m^2 less annual eGFR decline during follow-up, and a 3% lower risk of the composite kidney outcome. Clear dose-response associations between coffee consumption and kidney outcomes were found. Associations between coffee consumption and kidney outcomes were generally consistent across different subgroups. Diabetes was a consistent effect modifier for both outcomes (annual change in eGFR and the composite kidney outcome), with stronger associations in individuals with diabetes than in those without diabetes.

Previous studies on the association between coffee consumption and kidney outcomes have been inconclusive. Among 14,209 US middle-aged adults from the Atherosclerosis Risk in Communities (ARIC) study, caffeinated coffee consumption was associated with a lower risk of incident CKD during 24 years of follow-up, with the largest benefit for those consuming >3 cups per day (19). In line with this, a study from Korea with 11 years follow-up showed that ≥2 cups/day of coffee consumption was associated with a lower risk of incident CKD and with less annual eGFR decline compared to those who drank <1 cup/day among 8717 participants (20). In contrast, no association was found between coffee and caffeine intake and incident CKD among 1780 generally healthy Iranian participants during six years of follow-up (22). Similarly, the Doetinchem Cohort Study found no significant association of coffee consumption (mainly caffeinated and filtered coffee) with annual eGFR changes or a rapid decline in eGFR among 4772 middle-aged adults over 15 years of follow-up (25). To our knowledge, only one study prospectively addressed the effects of coffee on kidney function. In a two-week clinical trial from Japan, coffee consumption increased cystatin-C-based eGFR in healthy young adults, suggesting a short term causal relationship (36). Our results are largely consistent with some of the findings that coffee consumption was beneficially associated with incident CKD and a rapid kidney function decline. In a previous study in Lifelines, we also identified coffee consumption as a beneficial component in the eGFR-related dietary patterns that was associated with a better kidney health (37). The discrepancy between our findings and results from the Doetinchem Cohort Study (25) might be explained by differences in methodology. In our study, the creatinine-based eGFR equation was used, whereas the combined creatinine-cystatin C-based eGFR equation was used in the Doetinchem Cohort Study. Moreover, the Doetinchem Cohort Study might have been underpowered to detect a relatively small effect of coffee consumption on kidney outcomes.

The association between higher coffee consumption and an increased eGFR may at least partly be explained by an effect on glomerular hyperfiltration. Previous studies found that higher coffee consumption can slightly increase blood pressure (38, 39). In turn, elevated blood pressure may lead to the glomerular hypertension, and subsequently to glomerular hyperfiltration. One previous study found a linear association between coffee consumption and hyperfiltration in the early stage of hypertension, especially in heavy drinkers (>3 cups) among 1106 young-to-middle-age hypertensive adults (40). Similarly, coffee consumption increased cystatin-C-based eGFR in the previously mentioned two-week clinical trial from Japan, which may also suggest a reflection of glomerular hyperfiltration (36). However, chronic hyperfiltration is considered deleterious and could contribute to CKD progression (41). This would be in contrast with the inverse association between coffee consumption and kidney outcomes in our study and previous studies (19, 20, 25). The Doetinchem Cohort Study found no significant association of coffee consumption with annual eGFR changes over 15 years of follow-up (25), which has a longer follow-up time than our study. Their result does not support the view that elevated eGFR is the result of compensatory hyperfiltration.

We performed subgroup analyses to explore potential effect modification. The magnitude and direction of associations between coffee consumption and kidney outcomes were generally similar across strata. We found that diabetes may modify the association between coffee and kidney function. The association was stronger in participants with diabetes than those without diabetes. Whether additives such as milk or sugar affect the associations between coffee consumption and kidney health is not clear. Nevertheless, moderate unsweetened coffee and sugar-sweetened coffee consumption were associated with similar reduction in the risk for mortality among 171,616 participants from the UK Biobank (42). In our study, 70% of coffee drinkers consumed coffee without sugar and 42% consumed coffee without adding any types of milk. The association between coffee consumption and kidney outcomes were similar after additional adjustment for added sugar and milk in coffee (data were not shown).

It is unclear which specific bioactive compounds in coffee could influence kidney function. Coffee contains numerous substances, such as caffeine, chlorogenic acids, diterpenes, cafestol, kahweol, trigonellin, and polyphenols. Caffeine is a natural methylxanthine that can non-selectively block A1 adenosine receptors on distal afferent arterioles (43). Thus, caffeine may prevent afferent arteriolar constriction leading to the glomerular hyperfiltration and higher eGFR (44). Yet, as discussed above, this would be more difficult to align with better kidney outcomes. Furthermore, both caffeinated and decaffeinated coffee consumption have been associated with a reduced risk of all-cause mortality (12) and incidence of diabetes (13), suggesting that other compounds in coffee may also affect human health. Further studies are needed to investigate the differences between the associations of caffeinated and decaffeinated coffee consumption with kidney outcomes.

Other coffee components such as phenolic compounds, diterpenes, trigonelline, and melanoidins have anti-inflammatory and anti-oxidative effects (10, 11), which could beneficially affect kidney function. One study identified three coffee-related serum metabolites (glycochenodeoxycholate, O-methylcatechol sulfate and 3-methyl catechol sulfate) that were associated with incident CKD (45). Among these, glycochenodeoxycholate might favorably impact kidney health, while O-methylcatechol sulfate and 3-methyl catechol sulfate might represent potential harmful components of coffee on kidney health, suggesting a combination of beneficial and detrimental effects of coffee consumption on kidney health. Mendelian randomization studies identified genetic variation in caffeine metabolism indicating slower or faster caffeine metabolism, but genetic variation did not modify associations between coffee consumption and all-cause or cardiovascular mortality in the UK Biobank (46). In the same cohort, one study identified genetic variants associated with daily cups of coffee consumption and suggested a causal relationship between genetically predicted high coffee consumption and a reduced risk of CKD among regular coffee drinkers in the UK Biobank population (47, 48).

Strengths of our study include its prospective design, community-based population, and large sample size, which enabled us to perform subgroup analyses with sufficient power and which enhances generalisability. Some limitations of this study also need to be addressed. First, we could not distinguish the association of caffeinated and decaffeinated coffee with kidney outcome because types of coffee, such as caffeinated vs decaffeinated coffee and filtered vs unfiltered coffee, were not specifically asked for in the Lifelines FFQ. Given coffee consumption habits in the Dutch populations, most consumed coffee is likely to be caffeinated and filtered coffee (30). Second, residual confounding might still be present, despite careful adjustment for a wide range of confounders. Third, creatinine-based eGFR was used in this study, while cystatin C might be more sensitive to kidney function independent of muscle mass (49). Since no data on cystatin C or albuminuria, a marker of kidney damage, were available in Lifelines, more studies are needed to confirm these findings using the combined creatinine-cystatin C-based eGFR equation and albuminuria. Fourth, given the observational nature of this study, a causal relationship cannot be established with these data alone.

In summary, this large population-based study in Dutch adults shows that higher coffee consumption is associated with less kidney function decline in a dose-response manner. Higher coffee consumption was also associated with a lower risk of incident CKD or a rapid kidney function decline. Our findings support the idea that coffee consumption can be part of a healthy diet, at least regarding kidney health. Further studies are needed to address potential causality and understand the underlying mechanisms.

Disclosure

The authors declare no relevant financial interests.

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Supplemental Table 1 Association between daily coffee consumption and annual change in eGFR during follow-up among coffee drinkers in the Lifelines Cohort.

	Coffee consumption (cups/day) β (95% CI)					Per cup increment of coffee consumption	
	>0-2	>2-4	>4-6	>6	P_{trend}	β (95% CI)	P-value
Annual change in eGFR (mean ± SD), mL/min per 1.73 m^{2} #	-2.51 ± 2.78	-2.40 ± 2.63	-2.40 ± 2.60	-2.35 ± 2.62	<0.001		
Model 1	Reference	0.05 (0.01, 0.11)	0.11 (0.05, 0.17)	0.12 (0.05, 0.20)	<0.001	0.02 (0.01, 0.04)	<0.001
Model 2	Reference	0.07 (0.01, 0.12)	0.14 (0.08, 0.20)	0.17 (0.09, 0.25)	<0.001	0.03 (0.02, 0.04)	<0.001
Model 3	Reference	0.05 (0.01, 0.10)	0.10 (0.04, 0.16)	0.15 (0.08, 0.23)	<0.001	0.03 (0.02, 0.04)	<0.001

Model 1. Adjusted for age and sex. Model 2. Model 1 plus education level, physical activity, smoking, alcohol intake, total energy intake, intake of sugar-sweetened beverages, red and processed meat, dairy products, fruits and vegetables, and tea intake. Model 3. Model 2 plus baseline eGFR, systolic BP, and BMI. **#** Mean value of annual change in eGFR based on the categories of coffee consumption without adjustment. eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; CI, confidence interval; SD, standard deviation; BP, blood pressure; BMI, body mass index.

Supplemental Table 2 Association between daily coffee consumption and annual change in eGFR during follow-up among 78,346 participants free of CKD at baseline in the Lifelines Cohort.

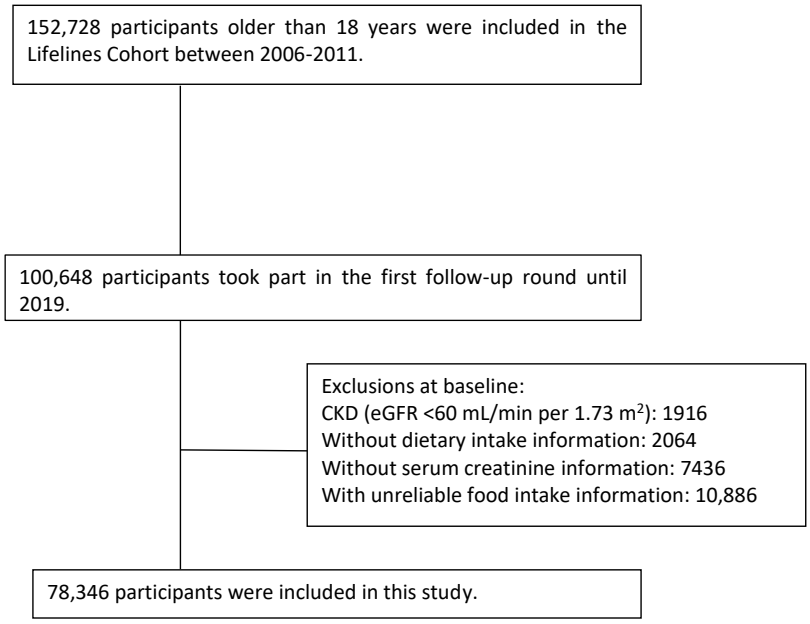
	Coffee consumption (cups/day) β (95% CI)						Per cup increment of coffee consumption	
	0	>0-2	>2-4	>4-6	>6	P_{trend}	β (95% CI)	P-value
Annual change in eGFR (mean ± SD), mL/min per 1.73 m^{2} #	-2.86 ± 2.96	-2.51 ± 2.78	-2.40 ± 2.63	-2.40 ± 2.60	-2.35 ± 2.62	<0.001		
Model 1	Reference	0.19 (0.11, 0.26)	0.24 (0.17, 0.31)	0.30 (0.22, 0.37)	0.31 (0.22, 0.40)	<0.001	0.03 (0.02, 0.04)	<0.001
Model 2	Reference	0.20 (0.13, 0.28)	0.26 (0.19, 0.34)	0.33 (0.25, 0.41)	0.36 (0.26, 0.46)	<0.001	0.04 (0.03, 0.05)	<0.001
Model 3	Reference	0.15 (0.07, 0.22)	0.19 (0.11, 0.26)	0.24 (0.16, 0.32)	0.29 (0.20, 0.38)	<0.001	0.03 (0.02, 0.04)	<0.001

Model 1. Adjusted for age and sex. Model 2. Model 1 plus education level, physical activity, smoking, alcohol intake, total energy intake, intake of sugar-sweetened beverages, red and processed meat, dairy products, fruits and vegetables, and tea intake. Model 3. Model 2 plus baseline eGFR, systolic BP, and BMI. **#** Mean value of annual change in eGFR based on the categories of coffee consumption without adjustment. eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; CI, confidence interval; SD, standard deviation; BP, blood pressure; BMI, body mass index.

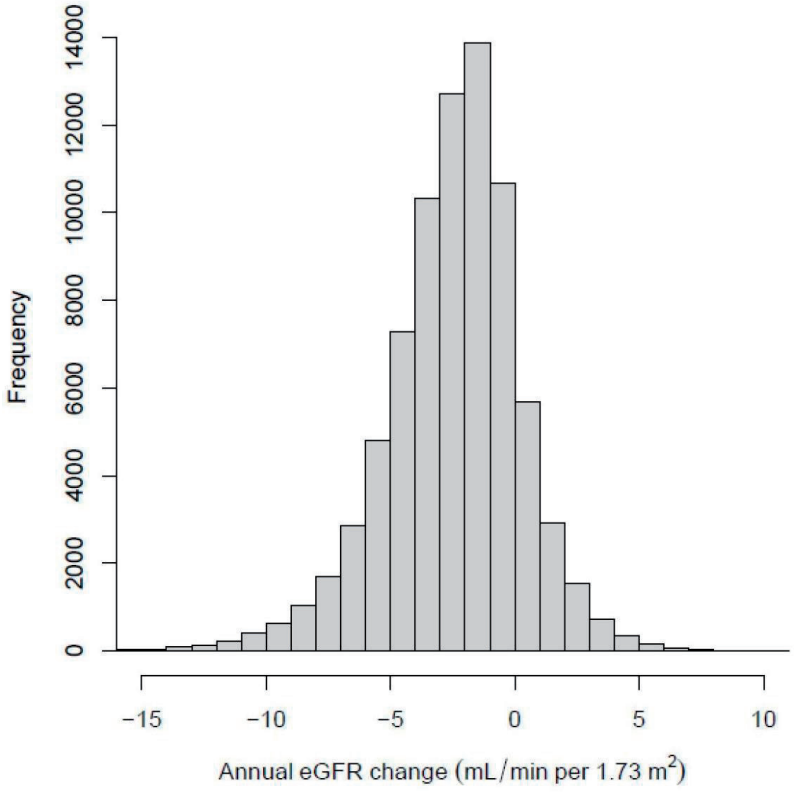
Supplemental Table 3 Association between daily coffee consumption and risk of composite kidney outcome (incident CKD or eGFR decline>20%) during follow-up among 78,346 participants free of CKD at baseline in the Lifelines Cohort.

	Coffee consumption (cups/day) OR (95% CI)						Per cup increment of coffee consumption	
	0	>0-2	>2-4	>4-6	>6	P_{trend}	OR (95% CI)	P-value
Events/Number	856/7816	1809/15,945	3295/28,396	1983/18,474	792/7715	0.029		
Model 1	Reference	0.94 (0.86, 1.02)	0.89 (0.82, 0.97)	0.85 (0.78, 0.93)	0.87 (0.78, 0.97)	<0.001	0.98 (0.97, 0.99)	<0.001
Model 2	Reference	0.92 (0.84, 1.01)	0.87 (0.79, 0.95)	0.83 (0.75, 0.91)	0.84 (0.75, 0.95)	<0.001	0.98 (0.96, 0.99)	<0.001
Model 3	Reference	0.91 (0.83, 0.99)	0.85 (0.78, 0.93)	0.81 (0.74, 0.89)	0.83 (0.74, 0.93)	<0.001	0.97 (0.96, 0.99)	<0.001

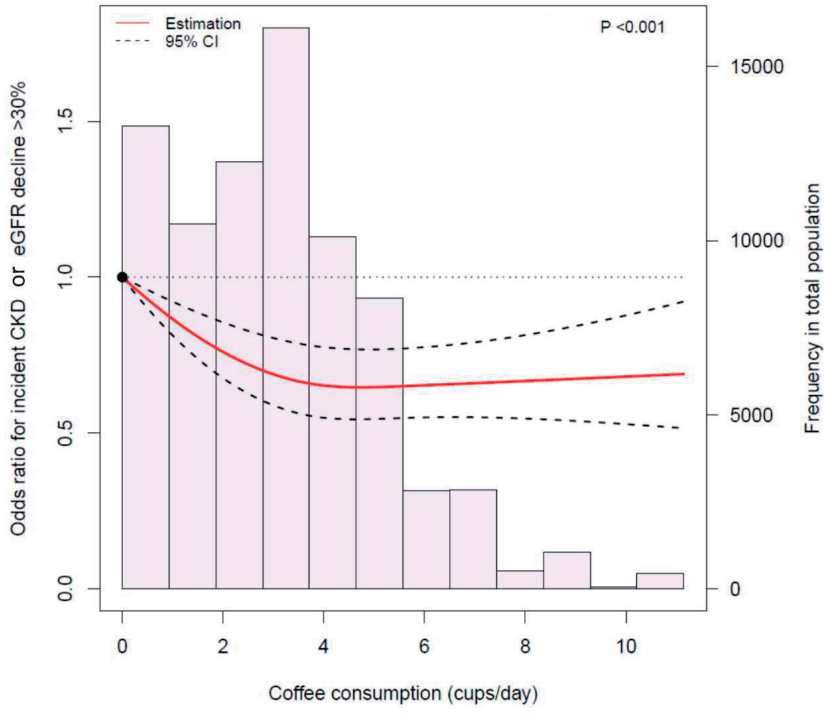
Model 1. Adjusted for age and sex. Model 2. Model 1 plus education level, physical activity, smoking, alcohol intake, total energy intake, intake of sugar-sweetened beverages, red and processed meat, dairy products, fruits and vegetables, and tea. Model 3. Model 2 plus baseline eGFR, systolic BP, and BMI. eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; CI, confidence interval; BP, blood pressure; BMI, body mass index.



Supplemental Fig. 1 Flowchart of participants selection. CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.



Supplemental Fig. 2 Distribution of annual change in eGFR. eGFR, estimated glomerular filtration rate.



Supplemental Fig. 3 Prospective associations between coffee consumption (cups/day) and composite kidney outcome (incident CKD or a >30% eGFR decline) among 78,346 participants free of CKD in the Lifelines Cohort. Data were fit by multivariable logistic regression with 3-knot restricted cubic spline using non-coffee consumers as the reference (odds ratio=1). Overall association between coffee consumption and the composite kidney outcome: P<0.001. Model was adjusted for age, sex, education level, physical activity, smoking, alcohol intake, total energy intake, intake of sugar-sweetened beverages, red and processed meat, dairy products, fruits and vegetables, tea, baseline eGFR, systolic BP, and BMI. CKD, chronic kidney disease; BMI, body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate.

Chapter 6

Dairy products and kidney function decline after myocardial infarction: a prospective analysis in the Alpha Omega Cohort

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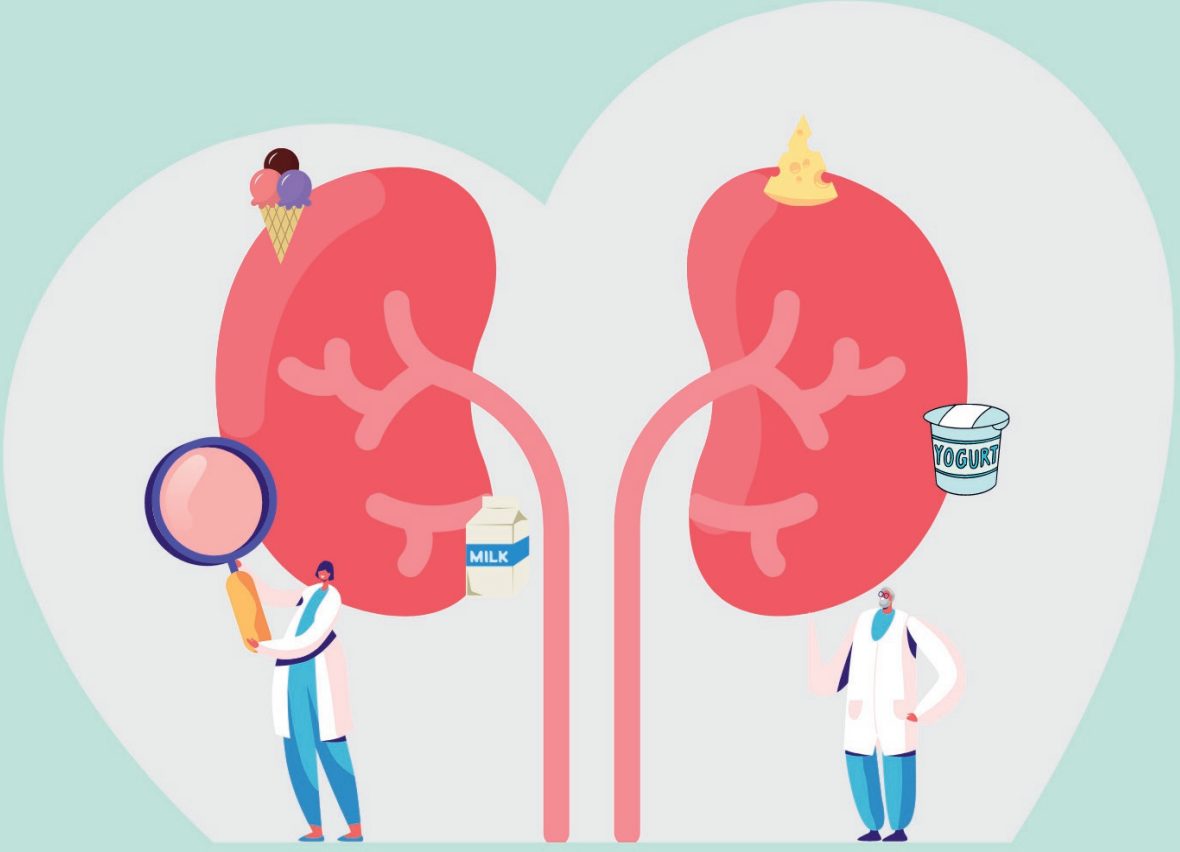

Abstract

Background & aims Population-based studies have shown both beneficial and neutral associations between dairy consumption and kidney function outcomes. We investigated the association between dairy products and kidney function decline in drug-treated post-myocardial infarction (MI) patients.

Methods We analysed data of 2169 post-MI patients (aged 60-80 years, 81% male) of the Alpha Omega Cohort. Dietary data were collected at baseline (2002-2006) using a validated 203-item food frequency questionnaire. The 2021 Chronic Kidney Disease Epidemiology (CKD-EPI) equation was used to estimate 40-months change in creatinine-cystatin C based glomerular filtration rate ($eGFR_{cr\text{-}cysC}$, mL/min per 1.73 m^2). Beta coefficients and 95% confidence intervals (CIs) for dairy products in relation to annual $eGFR_{cr\text{-}cysC}$ change were obtained from multivariable linear regression, adjusted for age, sex, energy intake, and other lifestyle and dietary factors.

Results Baseline energy-adjusted median intakes were 64 grams/day for total milk, 20 grams/day for hard cheeses, 18 grams/day for plain yoghurt, and 70 grams/day for dairy desserts. Mean ± SD $eGFR_{cr\text{-}cysC}$ was 84 ± 20 (13% with CKD), and annual $eGFR_{cr\text{-}cysC}$ change was -1.71 ± 3.85. In multivariable models, high vs low intakes of total milk, cheese, and dairy desserts were not associated with annual $eGFR_{cr\text{-}cysC}$ change ($\beta_{total\ milk}$: -0.21 [-0.60;0.19], β_{cheese}: -0.08 [-0.52;0.36], $\beta_{dairy\ desserts}$: -0.24 [-0.72;0.24]). High vs low intake of yoghurt was adversely associated with annual $eGFR_{cr\text{-}cysC}$ change ($\beta_{total\ yoghurt}$: -0.50 [-0.91;-0.09]), but subsequent spline analyses showed no clear dose-response association.

Conclusions Intakes of milk, cheese or dairy desserts were not associated with a delayed kidney function decline after MI. The observed adverse association for yoghurt should be interpreted with caution. Our findings require confirmation in other cohorts of coronary heart disease patients.

Introduction

The estimated glomerular filtration rate (eGFR) is commonly used to assess kidney function, which declines with an average rate of 8 mL/min per 1.73 m^2 per decade starting around age 35 years (1). In patients with established cardiovascular disease (CVD), kidney function decline is accelerated (2, 3), and they are thus at higher risk of chronic kidney disease (CKD). In post-myocardial infarction (MI) patients of the Alpha Omega Cohort, having an eGFR of 30-59 mL/min per 1.73 m^2 (chronic kidney disease, CKD) was associated with 2-3-fold higher risk of premature mortality from CVD or other causes compared to patients with an eGFR >90 mL/min per 1.73 m^2 (4). A healthier diet could potentially lower the risk of CKD in CVD patients.

Adherence to healthy diets have been consistently associated with lower risk of adverse kidney function outcomes (5), and with lower risk of CKD progression and mortality in patients diagnosed with CKD (6), also in drug-treated post-MI patients of the Alpha Omega Cohort (7). Among various dietary factors, particularly low-fat dairy products have been associated with lower risk of CKD, yet this beneficial association was not present in all studies (5, 8, 9). Dairy, a major component of the Western diet, is a heterogenous food matrix, consisting of micronutrients (e.g. calcium, potassium, magnesium), macronutrients (e.g. protein), and fatty acids (mainly saturated fatty acids [SFAs] and *trans* fatty acids). These nutrients may exert contrasting effects on kidney health. Several micronutrients in dairy have been related to lower blood pressure (10), reduced insulin resistance (11), lower levels of inflammation (12), and improved kidney function outcomes (13). Nevertheless, dairy is also high in protein and adults with CKD at risk of progression are advised to limit their daily protein intake to <1.30 g/kg body weight (14), to prevent CKD progression and glomerular hyperfiltration (15). Furthermore, SFAs and *trans* fatty acids are associated with elevated LDL cholesterol levels (16, 17).

In the Alpha Omega Cohort, we previously observed that total dairy intake and dairy products were not associated with diabetes risk (18) or with cause-specific mortality (19). Intake of yoghurt, however, was associated with a 4% lower risk of CVD mortality per increment of 25 grams/day (19). In the current study, we evaluated the association between habitual intake of milk, cheese, yoghurt, and dairy desserts, and kidney function decline in post-MI patients of the Alpha Omega Cohort.

Materials & Methods

Study design and Patients

We used data of the Alpha Omega Cohort. The cohort consists of 4837 drug-treated Dutch patients (aged 60-80 years, approximately 80% men) with a verified history of MI <10 years

before study enrolment (2002-2006). Follow-up for cause-specific mortality is still ongoing. The medical ethics committee of the Haga Hospital (The Hague, the Netherlands) approved the study as well as ethics committees of participating hospitals. All patients provided oral and written informed consent.

For the current study, patients were eligible if they provided a blood sample at baseline and after ~40 months (n=2488). We excluded patients with incomplete eGFR assessment (n=148), incomplete dietary data (n=164), and with implausibly high or low energy intakes (<800 or >8000 kcal/day for men, <600 or >6000 kcal/day for women; n=7), which yielded 2169 patients for the analysis (**Supplemental Fig. 1**).

Dietary assessment

A validated 203-item semi-quantitative food frequency questionnaire (FFQ) was used to assess habitual dietary intake at baseline. This FFQ was an extended version of a previously validated and reproducible FFQ, specifically designed to estimate fatty acids and cholesterol intake (20, 21). A Pearson's correlation coefficient of 0.83 was calculated for total energy intake measured by the FFQ and a dietary history (20), indicating high validity (21). High reproducibility was found for repeated measurements of the FFQ for specific dairy products (Spearman's correlation coefficients of 0.69 for cheese and 0.80 for a combination of milk, yoghurt and custard (20, 21)). Dairy intake was estimated from the FFQ in grams/day and grouped by fat content. Butter, milk and creamers from non-dairy sources, such as soy-milk, were not included in this study. Specific dairy products were grouped as follows: total milk, low-fat milk, hard cheeses, total (plain) yoghurt, low-fat yoghurt, and dairy desserts, according to previous Alpha Omega Cohort studies (**Supplemental Table 1)** (18, 19). Daily intake of total energy (kcal/day) and nutrients ([milli]grams/day) was calculated by using the 2006 Dutch Food Composition Table (NEVO 2006), that was most recent at the time of exposure (2002-2006) (22).

Kidney function assessment

At baseline and after ~40 months of follow-up, both creatinine and cystatin C were measured from stored blood samples in a central laboratory, as described in detail elsewhere (23). Serum creatinine was assessed by using the modified kinetic Jaffé method and serum cystatin C was measured by a particle-enhanced immunonephelometric assay. We estimated GFR based on creatinine and cystatin C ($eGFR_{cr\text{-}cysC}$) at baseline and ~40 months follow-up, using the updated Chronic Kidney Disease Epidemiology Collaboration equations from 2021 (24). Annual $eGFR_{cr\text{-}cysC}$ change was calculated by subtracting a patient's baseline $eGFR_{cr\text{-}cysC}$ from their follow-up $eGFR_{cr\text{-}cysC}$ and dividing the result by the patient's specific follow-up time in years. Negative beta coefficients indicate more kidney function decline and positive beta coefficients indicate less kidney function decline. For the main analyses, we use annual change in $eGFR_{cr\text{-}cysC}$ as outcome. Additional results for change in $eGFR_{cysC}$ are reported in the

supplement. Baseline $eGFR_{cr\text{-}cysC}$ <60 mL/min per 1.73 m^2 was used as proxy of prevalent CKD, according to KDIGO guidelines (25).

Covariates

Information on sociodemographic factors, including education, was obtained from self-administered questionnaires. Highest level of attained education was grouped in three categories: low, intermediate and high. Smoking status was categorised as never, former, current. Physical activity was assessed by the validated Physical Activity Scale for the Elderly (26), and reported in three categories: low (no or only light activity, ≤3 metabolic equivalent tasks [METs]), intermediate (>0 - <5 days/week of moderate or vigorous activity, >3 METs), or high (≥5 days/week of moderate or vigorous activity, >3 METs).

Information about intake of alcoholic beverages was obtained from the FFQ, from which alcohol consumption (grams/day) was calculated using the 2006 Dutch Food Composition Table (NEVO 2006). Alcohol consumption was then categorised as no (0 grams/day), low (>0-10 grams/day), moderate (women: >10-20 grams/day; men: >10-30 grams/day), or high intake (women: >20 grams/day; men: >30 grams/day). Other dietary covariates (grams/day) were derived from the FFQ, of which the following food groups were composed: fruits, vegetables, whole grains, refined grains, red-and processed meat, sugar-sweetened beverages (SSBs), coffee (caffeinated and decaffeinated) tea, fish, and sodium.

Blood lipids (total cholesterol, HDL cholesterol, LDL cholesterol and triglycerides) and glucose levels were determined by using a Hitachi 912 Autoanalyser (Roche Diagnostics, Basel, Switzerland) (27). In about 50% of the cohort, blood was collected in a fasting state. Prevalent diabetes mellitus was defined as a self-reported physician's diagnosis, use of glucose lowering drugs, or elevated plasma glucose level (≥7.0 mmol/L if fasted for ≥4 h or ≥11.1 mmol/L if not fasted).

Body mass index (BMI) was calculated by measured weight (kg) divided by the squared height (m^2), and obesity was defined as BMI ≥30 kg/m^2. Systolic and diastolic blood pressure was an average of two measurements on the left arm in seated position using an automated device (Omron HEM-711) following a 10-min rest. Hypertension was defined as high blood pressure (systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg) or use of antihypertensive drugs. Medication was self-reported and coded according to the Anatomical Therapeutic Chemical (ATC) Classification System: antihypertensive drugs (CO2, C03, C07, C08, and C09), anti-thrombotic drugs (B01), statins (C10AA and C10B), and renin-angiotensin-aldosterone system (RAAS) blockers (C09) (28).

Statistical analysis

Baseline characteristics were described as means (standard deviations, SD) for normally distributed data, median (interquartile range, IQR) for skewed variables, and n (%) for categorical data, for both the total population and across categories of total milk consumption. All dairy groups were energy-adjusted by using the residual method (29).

We used multivariable linear regression to study associations of baseline dairy product intake with annual $eGFR_{cr\text{-}cysC}$ change. To address potential non-linearity, we first analysed associations using restricted cubic splines (RCS, knots located at 10^{th}, 50^{th}, and 90^{th} percentile). The associations were visualised in graphs. Although figures were restricted to showing energy-adjusted intakes >0 to ≤400 grams/day (total milk and low-fat milk), >0 to ≤80 grams/day (cheese), and >0 to ≤200 grams/day (total yoghurt, low-fat yoghurt, and dairy desserts), analyses also included extremely low and extremely high intakes. We additionally used multivariable linear regression (β with 95% confidence intervals [CIs]) to analyse associations of baseline dairy products intake per 1-SD increment and in categories (lowest intake as reference) with annual $eGFR_{cr\text{-}cysC}$ change. Based on sample size, we created the following categories of dairy products intake (grams/day): total milk, including low-fat milk (<25, ≥25-125, ≥125), hard cheese (<15, ≥15-30, ≥30), total yoghurt, including low-fat yoghurt (<10, ≥10-60, ≥60), and dairy-based desserts (<50, ≥50-100, ≥100). The P_{trend} was obtained by treating the categories as a continuous variable in the models.

For all analyses, we created three models for confounder adjustment and all confounders were selected *a priori* based on previous literature. In model one, we adjusted for age, sex, and total energy intake. In model two, we additionally added smoking status (never, former, current), physical activity (low, intermediate, high), education (low, intermediate, high), alcohol intake (abstainers, low, moderate, high), obesity (yes, no), and RAAS medication (yes, no) as potential confounders. In the final model, model three, daily intake of dietary factors, including grains, fruits, vegetables, red-and processed meat, SSBs, coffee, tea, sodium, and fish were included. Missing data of covariates, which ranged from 0.09% to 0.51%, were imputed with sex-specific means (normally distributed variables) and modes (categorical variables).

To explore the role of sex, diabetes, obesity, and CKD, we performed both subgroup and sensitivity analyses using model three. Subgroup analyses were conducted per 1-SD increment of the specific dairy product, for reasons of power. Sensitivity analyses were conducted by repeating the categorical analyses after excluding women, patients with diabetes or obesity. The role of CKD was studied, since potassium and protein, major components of dairy products, may have contradictive effects on kidney function decline, depending on eGFR stage (30-32). We also repeated analyses by using annual change in $eGFR_{cysC}$ as an outcome, because protein from dairy could have affected serum creatinine.

Finally, we performed three distinct exploratory analyses. First, analyses for specific dairy products were additionally adjusted for other dairy products, to assure an independent association of a certain dairy type. Secondly, we additionally adjusted for total serum cholesterol, serum triglycerides, and presence of hypertension, since these factors may be potential intermediates of the dairy-kidney association. Thirdly, we additionally adjusted model three for baseline $eGFR_{cr\text{-}cysC}$.

Results

Baseline characteristics

The baseline characteristics for 2169 post-MI patients and according to categories of energy-adjusted total milk consumption, are described in **Table 1**. Patients were on average 69 ± 5 years old, and predominantly male (81%). Most patients used antithrombotic drugs, antihypertensives, and statins. Those with the highest milk intake were more often physically active, a never smoker, and consumed less alcohol, than patients with the lowest milk intake. They were more often obese or diabetic compared to those with the lowest milk intake. At baseline, the mean ± SD $eGFR_{cr\text{-}cysC}$ was 84 ± 20 mL/min per 1.73 m^2 (13% with CKD) in the total population, and this proportion did not substantially differ across categories of milk intake. No major differences in dietary factors across categories of milk intake were observed (**Supplemental Table 2**).

Milk consumption and annual kidney function decline

Baseline median [IQR] energy-adjusted milk intake was 63.7 [1.1, 141.5] grams/day (**Supplemental Table 2**). The mean ± SD annual $eGFR_{cr\text{-}cysC}$ decline was 1.59 ± 3.98 mL/min per 1.73 m^2 in the lowest milk intake group, and this decline was slightly larger in the highest milk intake group (1.78 ± 3.74 mL/min per 1.73 m^2) (**Table 2**). After multivariate adjustment, milk intake was not associated with annual $eGFR_{cr\text{-}cysC}$ decline when analysed using RCS (**Fig. 1**), per 1-SD increment (**Supplemental Fig. 4),** or across categories (**Table 2**). Similar results were obtained for low-fat milk (**Table 2, Supplemental Fig. 2, Supplemental Fig. 8**).

Table 1 Baseline characteristics of 2169 patients of the Alpha Omega Cohort, overall, and by categories of total milk consumption.

		Energy-adjusted total milk consumption (grams/day)		
	Total population (n=2169)	<25 (n=822)	≥25-125 (n=667)	≥125 (n=680)
Sociodemographic factors				
Age, years	68.9 ± 5.4	68.7 ± 5.3	69.0 ± 5.5	69.0 ± 5.4
Men, n (%)	1752 (80.8)	688 (83.7)	524 (78.6)	540 (79.4)
Education, n (%)				
Low	1225 (56.5)	453 (55.1)	364 (54.6)	408 (60.0)
Intermediate	671 (30.9)	251 (30.5)	227 (34.0)	193 (28.4)
High	263 (12.1)	113 (13.7)	72 (10.8)	78 (11.5)
Lifestyle factors				
Smoking status, n (%)				
Never	360 (16.6)	134 (16.3)	109 (16.3)	117 (17.2)
Former	1481 (68.3)	563 (68.5)	458 (68.7)	460 (67.6)
Current	328 (15.1)	125 (15.2)	100 (15.0)	103 (15.1)
Physical activity[a], n (%)				
Low	856 (39.5)	321 (39.1)	270 (40.5)	265 (39.0)
Intermediate	807 (37.2)	307 (37.3)	259 (38.8)	241 (35.4)
High	497 (22.9)	194 (23.6)	135 (20.2)	168 (24.7)
CVD (risk)factors				
Time since MI, years	4.0 [1.9, 6.4]	3.7 [1.9, 6.5]	4.4 [2.1, 6.6]	4.0 [1.9, 6.3]
BMI, kg/m^2	27.6 ± 3.6	27.4 ± 3.5	27.8 ± 3.6	27.7 ± 3.7
Obesity[b], n (%)	483 (22.3)	163 (19.8)	154 (23.1)	166 (24.4)
Serum blood lipids, mmol/L				
Total cholesterol	4.75 [4.19, 5.33]	4.72 [4.15, 5.33]	4.75 [4.20, 5.33]	4.77 [4.24, 5.34]
LDL cholesterol	2.72 ± 0.79	2.71 ± 0.78	2.71 ± 0.80	2.75 ± 0.79
Triglycerides	1.63 [1.21, 2.26]	1.61 [1.19, 2.25]	1.65 [1.21, 2.28]	1.63 [1.24, 2.27]
Fasting triglycerides[c]	1.45 [1.09, 1.93]	1.44 [1.08, 1.93]	1.48 [1.09, 1.93]	1.42 [1.11, 1.96]
Diabetes[d], n (%)	394 (18.2)	136 (16.5)	128 (19.2)	130 (19.1)
SBP, mmHg	144 ± 21	144 ± 21	145 ± 21	142 ± 21
DBP, mmHg	81.5 ± 10.7	81.2 ± 10.8	82.2 ± 10.5	81.2 ± 10.7
Hypertension[e], n (%)	2050 (94.5)	774 (94.2)	635 (95.2)	641 (94.3)
Medication[f], n (%)				
Statins	1857 (85.6)	705 (85.8)	576 (86.4)	576 (84.7)
Antihypertensives	1887 (87.0)	723 (88.0)	583 (87.4)	581 (85.4)

Table 1 continued

	Total population (n=2169)	Energy-adjusted total milk consumption (grams/day)		
		<25 (n=822)	≥25-125 (n=667)	≥125 (n=680)
RAAS blockers	1184 (54.6)	440 (37.2)	373 (31.5)	371 (31.3)
Antithrombotic agents	2127 (98.1)	811 (98.7)	654 (98.1)	662 (97.4)
Kidney function				
Serum creatinine, µmol/L	84.0 [72.0, 101.0]	86.0 [73.0, 104.0]	82.0 [71.0, 98.0]	83.0 [71.0, 99.0]
Serum cystatin C, mg/L	0.92 [0.82, 1.10]	0.91 [0.82, 1.08]	0.93 [0.82, 1.10]	0.91 [0.82, 1.10]
$eGFR_{cr\text{-}cysC}$, mL/min per 1.73 m^2	84.2 ± 19.5	83.9 ± 19.8	84.1 ± 19.1	84.7 ± 19.5
$eGFR_{cysC}$ [g], mL/min per 1.73 m^2	81.6 ± 19.5	82.0 ± 19.7	80.9 ± 19.2	81.8 ± 19.5
CKD[h], n (%)	273 (12.6)	99 (12.0)	93 (13.9)	81 (11.9)

Values are means ± standard deviation for normally distributed data, medians [interquartile range] for skewed data or n (%) for categorical data. Missing data were 0.5% for education, 0.4% for physical activity, 0.09% for BMI/obesity, 0.5% for total cholesterol, HDL cholesterol, and triglycerides, 5% for LDL cholesterol, 0.1% for SBP and DBP. [a] Low: no or only light activity (≤3 MET), moderate: >0–<5 days/week of moderate or vigorous activity (>3 MET), and high: ≥5 days/week of moderate or vigorous activity (>3 MET). [b] Defined as BMI ≥30 kg/m^2. [c] Based on sample size n=845. This sample size includes only patients who consumed their last meal ≥8h before blood sampling. Part of the cohort had missing values for fasting state (n=90). [d] Diabetes is considered present in case of a self-reported physician's diagnosis, use of glucose lowering drugs, or elevated plasma glucose level (≥7.0 mmol/L if fasted for ≥4 h or ≥11.1 mmol/L if not fasted). [e] Defined as SBP ≥ 140 mmHg or DBP ≥ 90 mmHg or use of antihypertensive drugs. [f] Anatomical Therapeutic Chemical Classification (ATC) System coding: statins (C10AA and C10B), anti-hypertensive drugs (C02, C03, C07, C08 and C09), antithrombotic drugs (B01), and RAAS blockers (C09). [g] Based on n=2247. Low milk intake: n=840, intermediate milk intake: n=692, high milk intake: n=715. [h] Defined as a single assessment of $eGFR_{cr\text{-}cysC}$ <60 mL/min per 1.73 m^2 at baseline. CVD, cardiovascular disease; MI, myocardial infarction; BMI, body mass index; LDL, low-density lipoprotein; HDL, high-density lipoprotein; SBP, systolic blood pressure; DBP, diastolic blood pressure; $eGFR_{cr\text{-}cysC}$, estimated glomerular filtration rate based on creatinine and cystatin C; RAAS, renin-angiotensin-aldosterone system; CKD, chronic kidney disease.

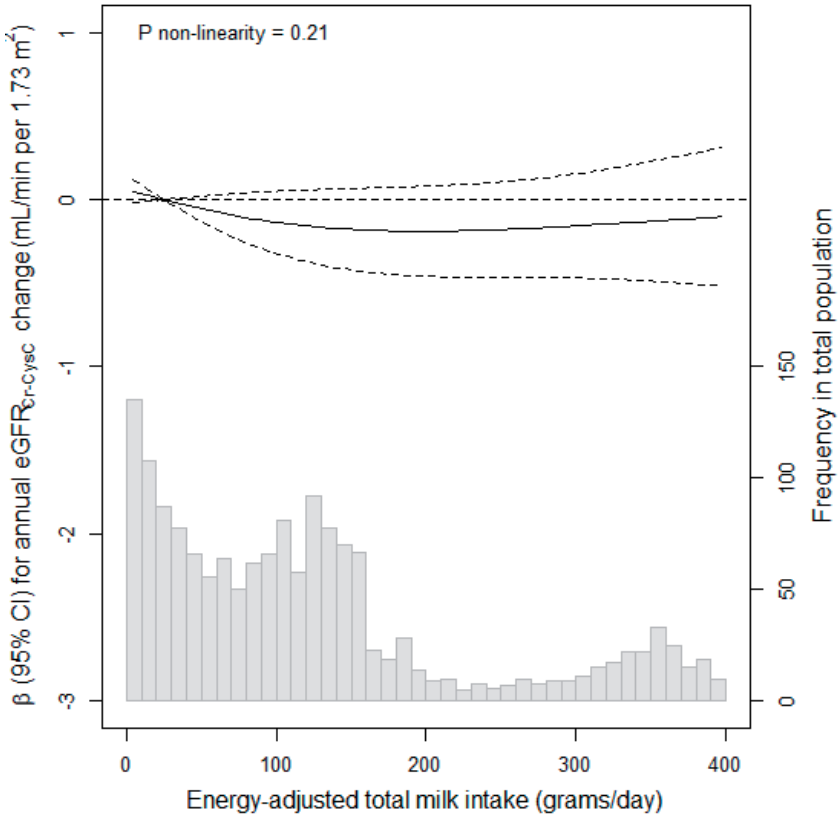

Fig. 1 Relationship between energy-adjusted total milk intake as continuous variable and annual $eGFR_{cr\text{-}cysC}$ change among 2169 patients of the Alpha Omega Cohort. Solid lines represent beta coefficients and dashed lines represent 95% CIs. Negative coefficients indicate more $eGFR_{cr\text{-}cysC}$ decline and positive coefficients indicate less $eGFR_{cr\text{-}cysC}$ decline. Three-knot restricted cubic splines was used, with an energy-adjusted intake of 25 grams/day as reference point. Betas were adjusted for age, sex, total energy intake, smoking status, physical activity, education, alcohol consumption, obesity, renin-angiotensin-aldosterone system blocking drugs, and dietary intake of whole grains, refined grains, fruits, vegetables, red- and processed meat, sugar sweetened beverages, coffee, tea, salt from foods, and fish. $eGFR_{cr\text{-}cysC}$, estimated glomerular filtration rate based on creatinine and cystatin C; CIs, confidence intervals.

Cheese consumption and annual kidney function decline

Baseline median [IQR] energy-adjusted intake of hard cheese was 19.5 [12.3, 32.1] grams/day (**Supplemental Table 2)** and the mean ± SD annual $eGFR_{cr\text{-}cysC}$ decline did not differ much across categories of hard cheese intake (**Table 2**). In line with this, no association was observed across categories of hard cheese intake (**Table 2**). However, results from RCS suggested a non-linear relationship (P non-linearity = 0.01), with more annual $eGFR_{cr\text{-}cysC}$ decline from energy-adjusted cheese intakes >60 grams/day (**Fig. 2**).

Yoghurt intake and annual kidney function decline

Baseline median [IQR] energy-adjusted intake of yoghurt was 17.9 [-11.7, 63.3] grams/day (**Supplemental Table 2)**. The mean ± SD annual $eGFR_{cr\text{-}cysC}$ decline was higher in the highest intake group (≥60 grams/day) than in the lowest intake group (<10 grams/day) (**Table 2**). This association remained in multivariable analyses of categories: patients with the highest intake (≥60 grams/day) had more annual $eGFR_{cr\text{-}cysC}$ decline (-0.50 [95% CI -0.91, -0.09] mL/min per 1.73 m^2, **Table 2**) than patients with the lowest intake (<10 grams/day). RCS suggested a non-linear relationship (P non-linearity = 0.03), with more annual $eGFR_{cr\text{-}cysC}$ decline and flattening of the curve for intakes >40 grams/day (**Fig. 3**). For low-fat yoghurt, comparable results were obtained (**Table 2, Supplemental Fig. 3**).

Table 2 Associations of energy-adjusted dairy subtypes and annual $eGFR_{cr\text{-}cysC}$ change in 2169 patients of the Alpha Omega Cohort.

	Energy-adjusted categories of dairy consumption, grams/day			
	Low	Intermediate	High	P_{trend} [a]
Total milk	<25 (n=822)	≥25-125 (n=667)	≥125 (n=680)	
Mean ± SD annual $eGFR_{cr\text{-}cysC}$ change, mL/min per 1.73 m^2	-1.59 ± 3.98	-1.77 ± 3.78	-1.78 ± 3.74	
Model 1[b]	Ref	-0.13 (-0.52;0.26)[e]	-0.16 (-0.55;0.34)	0.42
Model 2[c]	Ref	-0.14 (-0.54;0.25)	-0.17 (-0.57;0.22)	0.38
Model 3[d]	Ref	-0.14 (-0.53;0.26)	-0.21 (-0.60;0.19)	0.31
Low-fat milk	<25 (n=993)	≥25-125 (n=622)	≥125 (n=554)	
Mean ± SD annual $eGFR_{cr\text{-}cysC}$ change, mL/min per 1.73 m^2	-1.63 ± 3.95	-1.75 ± 3.74	-1.79 ± 3.79	
Model 1	Ref	-0.11 (-0.50;0.27)	-0.15 (-0.55;0.25)	0.44
Model 2	Ref	-0.13 (-0.52;0.25)	-0.18 (-0.58;0.22)	0.35
Model 3	Ref	-0.12 (-0.51;0.26)	-0.20 (-0.60;0.21)	0.32
Hard cheese	<15 (n=737)	≥15-30 (n=837)	≥30 (n=595)	
Mean ± SD annual $eGFR_{cr\text{-}cysC}$ change, mL/min per 1.73 m^2	-1.65 ± 3.71	-1.75 ± 3.97	-1.71 ± 3.85	
Model 1	Ref	-0.002 (-0.39;0.39)	-0.05 (-0.46;0.37)	0.82
Model 2	Ref	-0.002 (-0.39;0.39)	-0.06 (-0.47;0.36)	0.79
Model 3	Ref	-0.003 (-0.40;0.39)	-0.08 (-0.52;0.36)	0.73
Total yoghurt	<10 (n=931)	≥10-60 (n=645)	≥60 (n=593)	
Mean ± SD annual $eGFR_{cr\text{-}cysC}$ change, mL/min per 1.73 m^2	-1.42 ± 3.76	-1.96 ± 3.88	-1.87 ± 3.93	
Model 1	Ref	-0.54 (-0.93;-0.16)	-0.43 (-0.82;-0.03)	0.02
Model 2	Ref	-0.60 (-0.99;-0.21)	-0.49 (-0.89;-0.09)	0.009
Model 3	Ref	-0.60 (-0.99;-0.21)	-0.50 (-0.91;-0.09)	0.009
Low-fat yoghurt	<10 (n=1122)	≥10-60 (n=513)	≥60 (n=534)	
Mean ± SD annual $eGFR_{cr\text{-}cysC}$ change, mL/min per 1.73 m^2	-1.47 ± 3.74	-2.00 ± 3.93	-1.93 ± 3.96	
Model 1	Ref	-0.56 (-0.96;-0.16)	-0.45 (-0.85;-0.06)	0.01
Model 2	Ref	-0.61 (-1.01;-0.20)	-0.49 (-0.89;-0.09)	0.006
Model 3	Ref	-0.58 (-0.99;-0.18)	-0.50 (-0.90;-0.09)	0.006

Table 2 continued

	Energy-adjusted categories of dairy consumption, grams/day			
	Low	Intermediate	High	P_{trend} [a]
Dairy desserts	<50 (n=603)	≥50-100 (n=1064)	≥100 (n=502)	
Mean ± SD annual $eGFR_{cr\text{-}cysC}$ change, mL/min per 1.73 m^2	-1.44 ± 3.79	-1.91 ± 3.93	-1.61 ± 3.70	
Model 1	Ref	-0.39 (-0.79;0.01)	-0.06 (-0.52;0.40)	0.73
Model 2	Ref	-0.45 (-0.85;-0.05)	-0.13 (-0.60;0.35)	0.55
Model 3	Ref	-0.46 (-0.87;-0.06)	-0.24 (-0.72;0.24)	0.28

[a] P_{trend} was assessed by treating the categorical variable as a continuous variable in the model. [b] Model one included age, sex, and total energy intake. [c] Model two was additionally adjusted for smoking status (never, former, current), physical activity (low, intermediate, high), education (low, intermediate, high), alcohol consumption (abstainers, low, moderate, high), obesity (yes, no), and renin-angiotensin-aldosterone system blocking drugs (yes, no). [d] Model three was additionally adjusted for dietary intakes of whole grains, refined grains, fruits, vegetables, red- and processed meat, sugar sweetened beverages, coffee, tea, salt from foods, and fish intake (yes, no). [e] β (95% confidence interval) obtained from multivariable linear regression models (all such values). $eGFR_{cr\text{-}cysC}$, estimated glomerular filtration rate based on creatinine and cystatin C; SD, standard deviation.

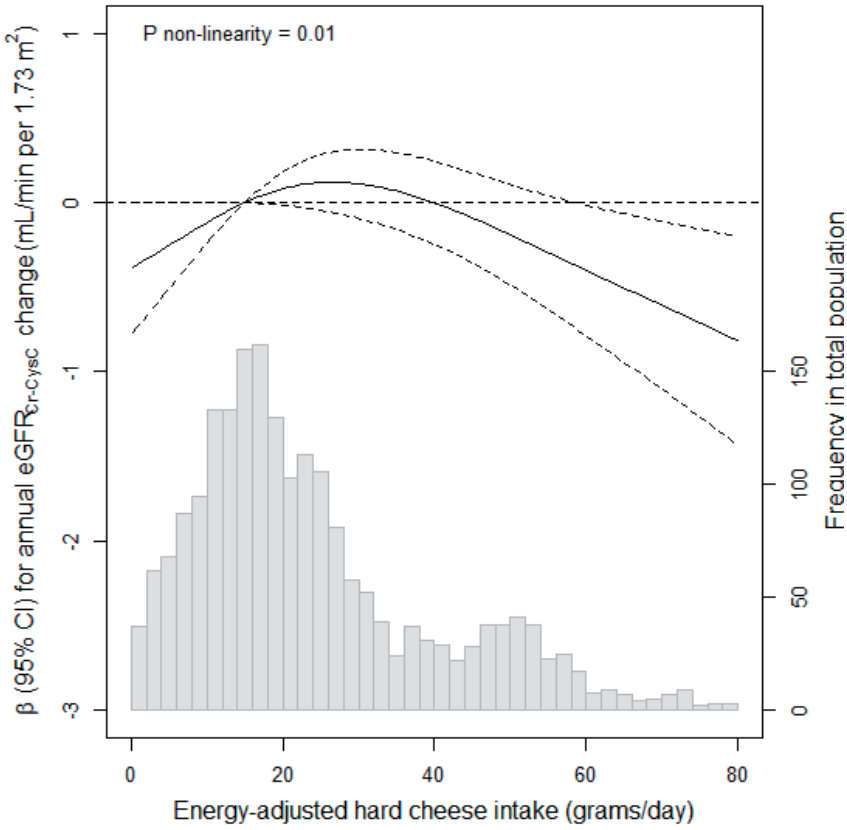

Fig. 2 Relationship between energy-adjusted intake of hard cheese as continuous variable and annual $eGFR_{cr\text{-}cysC}$ change among 2169 patients of the Alpha Omega Cohort. Solid lines represent beta coefficients and dashed lines represent 95% CIs. Negative coefficients indicate more $eGFR_{cr\text{-}cysC}$ decline and positive coefficients indicate less $eGFR_{cr\text{-}cysC}$ decline. Three-knot restricted cubic splines was used, with an energy-adjusted intake of 15 grams/day as reference point. Betas were adjusted for age, sex, total energy intake, smoking status, physical activity, education, alcohol consumption, obesity, renin-angiotensin-aldosterone system blocking drugs, and dietary intake of whole grains, refined grains, fruits, vegetables, red- and processed meat, sugar sweetened beverages, coffee, tea, salt from foods, and fish. $eGFR_{cr\text{-}cysC}$, estimated glomerular filtration rate based on creatinine and cystatin C; CIs, confidence intervals.

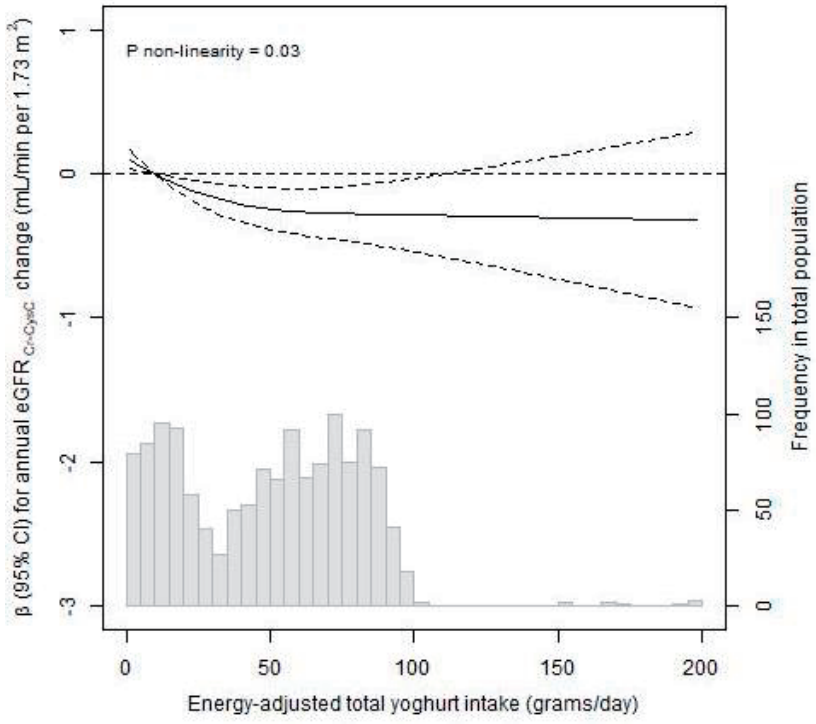

Fig. 3 Relationship between energy-adjusted intake of total yoghurt as continuous variable and annual $eGFR_{cr\text{-}cysC}$ change among 2169 patients of the Alpha Omega Cohort. Solid lines represent beta coefficients and dashed lines represent 95% CIs. Negative coefficients indicate more $eGFR_{cr\text{-}cysC}$ decline and positive coefficients indicate less $eGFR_{cr\text{-}cysC}$ decline. Three-knot restricted cubic splines was used, with an energy-adjusted intake of 10 grams/day as reference point. Betas were adjusted for age, sex, total energy intake, smoking status, physical activity, education, alcohol consumption, obesity, renin-angiotensin-aldosterone system blocking drugs, and dietary intake of whole grains, refined grains, fruits, vegetables, red- and processed meat, sugar sweetened beverages, coffee, tea, salt from foods, and fish. $eGFR_{cr\text{-}cysC}$, estimated glomerular filtration rate based on creatinine and cystatin C; CIs, confidence intervals.

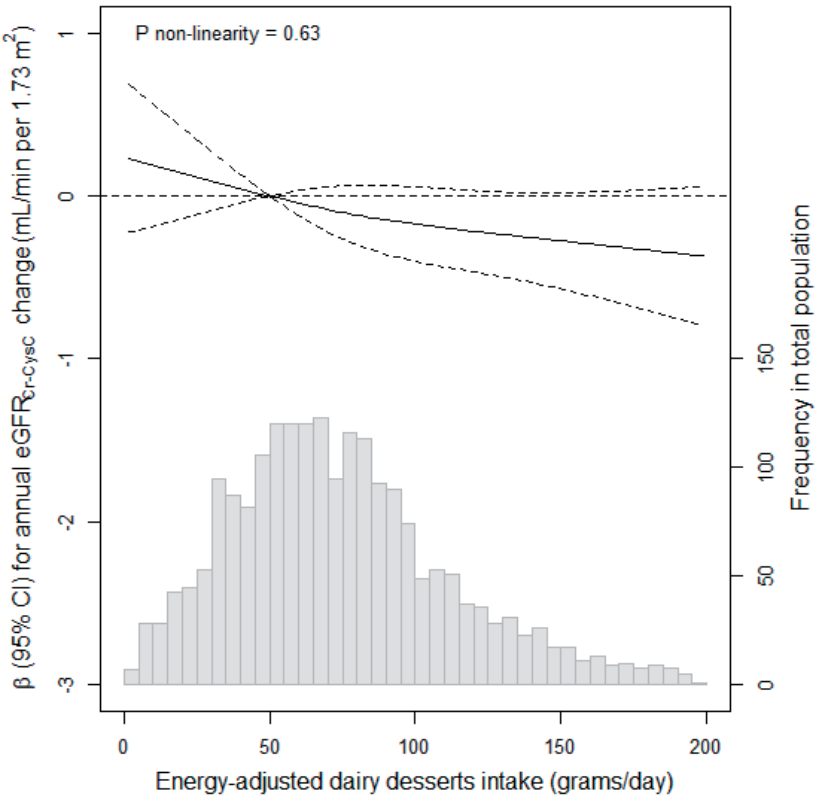

Fig. 4 Relationship between energy-adjusted intake of dairy desserts as continuous variable and annual $eGFR_{cr\text{-}cysC}$ change among 2169 patients of the Alpha Omega Cohort. Solid lines represent beta coefficients and dashed lines represent 95% CIs. Negative coefficients indicate more $eGFR_{cr\text{-}cysC}$ decline and positive coefficients indicate less $eGFR_{cr\text{-}cysC}$ decline. Three-knot restricted cubic splines was used, with an energy-adjusted intake of 50 grams/day as reference point. Betas were adjusted for age, sex, total energy intake, smoking status, physical activity, education, alcohol consumption, obesity, renin-angiotensin-aldosterone system blocking drugs, and dietary intake of whole grains, refined grains, fruits, vegetables, red- and processed meat, sugar sweetened beverages, coffee, tea, salt from foods, and fish. $eGFR_{cr\text{-}cysC}$, estimated glomerular filtration rate based on creatinine and cystatin C; CIs, confidence intervals.

Dairy desserts and annual kidney function decline

Baseline median [IQR] energy-adjusted intake of dairy desserts was 70.0 [47.5, 97.5] grams/day (**Supplemental Table 2**). In crude comparisons, patients with the highest intake of dairy desserts had slightly more annual $eGFR_{cr\text{-}cysC}$ decline than those with the lowest intake (**Table 2**). In multivariable models across categories, dairy desserts were not associated with annual $eGFR_{cr\text{-}cysC}$ decline (**Table 2**). In RCS, we found no indication of non-linear associations (P nonlinearity = 0.63, **Fig. 4**) and results of linear regression analyses per 1-SD increment also showed no statistically significant association (β -0.15 [95% CI -0.32;0.02]) (**Supplemental Fig. 7)**.

Sensitivity and subgroup analyses

Results for all dairy products remained largely similar after excluding women (**Supplemental Table 3**) and patients with comorbid conditions (**Supplemental Tables 4-6**). Additional adjustment for other dairy types, for CVD risk factors of the dairy-kidney association, or for baseline $eGFR_{cr\text{-}cysC}$ did not materially affect the results (**Supplemental Table 7**). When we used change in $eGFR_{cysC}$ as an outcome instead of change in $eGFR_{cr\text{-}cysC}$, we observed attenuated estimates towards the null for all dairy products, except for dairy desserts **(Supplemental Table 8**). Results for analyses per 1-SD increment were generally consistent across subgroups of sex, diabetes, CKD, and obesity (**Supplemental Fig. 4-9**). For dairy desserts, we observed a borderline significant association among 483 patients with obesity, with 0.31 mL/min per 1.73 m^2 (95% CI: -0.66;0.05) more kidney function decline per 1-SD increment (**Supplemental Fig. 7**).

Discussion

This prospective analysis among 2169 Dutch post-MI patients showed no association between intake of different dairy products and annual kidney function decline. The results for yoghurt are unclear, with RCS analysis showing more kidney function decline for energy-adjusted intakes until ~40 grams/day, and a flattened curve for higher intakes. The results for all dairy products were generally robust in all sensitivity and subgroup analyses.

Milk

To our knowledge, no previous studies on the relationship between milk and kidney function decline in cardiac patients have been performed. The population-based Dutch Doetinchem Cohort Study with a maximum of 15 years follow-up investigated associations between milk products (including all kinds of milk, yoghurt, coffee creamers, curd, pudding, porridge, custard, whipping cream) and annual eGFR decline, among 1488 participants with mildly decreased eGFR (mean ± SD eGFR of 99.2 ± 11.4 mL/min per 1.73 m^2). Contrary to our null findings, they observed less eGFR decline for ≥2 daily servings of milk products (33). In a recent study among 2416 CKD-free participants of the TLGS, low-fat milk was not associated with incident CKD after 8.4 years follow-up, whereas full-fat milk was associated with 3% lower risk of CKD (HR for 1-serving/week increment 0.97, 95% CI 0.94-0.99) (9). Differences could be explained by differences in study population (MI patients in Alpha Omega Cohort vs healthy individuals in Doetinchem Cohort Study and TLGS), the heterogenous food group (plain milk in Alpha Omega Cohort, various milk products in the Doetinchem Cohort Study and plain milk and chocolate milk in TLGS), or use of $eGFR_{cysC}$ (Doetinchem Cohort Study), or $eGFR_{cr}$ (TLGS) instead of $eGFR_{cr\text{-}cysC.}$ However, our sensitivity analysis also showed no associations of milk intake with annual $eGFR_{cysC}$ decline. Previous Alpha Omega Cohort studies have shown no association between total milk or low-fat milk intake and incident diabetes (18), a major

risk factor of kidney function decline, and CVD and coronary heart disease (CHD) mortality (19). These results corroborate our findings that, in CHD patients, consumption of milk is not associated with cardiometabolic outcomes, including kidney function.

Hard cheese and yoghurt

In the present study, high vs low intake of cheese was not associated with eGFR decline, in line with results of the previously mentioned Doetinchem Cohort Study (33). RCS plots in our study suggested that intakes ≥60 grams/day may be associated with additional annual eGFR decline, but the number of patients at these intake levels is small and more studies are needed to evaluate this. Cheese contributes to salt intake, which could explain additional kidney function decline in the larger intake ranges (34). Yoghurt was adversely associated with eGFR decline in our study. This result was unexpected, but could not be explained in various subgroup and sensitivity analyses. However, RCS showed no clear linear dose-response association, and we hypothesise that the observed adverse association with kidney function decline may be due to chance. The previously mentioned TLGS observed no association for low-fat and full-fat yoghurt intake in relation to CKD risk (9). Differences between the studies could be attributed to differences in study population. Previous Alpha Omega Cohort studies showed no association between yoghurt and diabetes risk (18), but yoghurt was favourably associated with CVD mortality risk (19). Therefore, our results for yoghurt in relation to kidney function should be interpreted with caution and require further study.

Dairy desserts

Intake of dairy desserts was not associated with kidney function decline, although a borderline significant adverse association was found in a subgroup of 483 patients with obesity. These results concur with results of a previous Alpha Omega Cohort study, which also showed no association with diabetes risk, and an adverse association in a subgroup of 685 patients with obesity (18). However, results in subgroups should be interpreted with caution, because of smaller sample sizes.

Total dairy vs dairy subgroups

Previous studies have mainly investigated total dairy or low-fat dairy, rather than dairy subtypes, in relation to kidney function. Contrary to our findings for dairy products, these studies have shown beneficial associations for total low-fat dairy (8), and null associations for total full-fat dairy (33, 35, 36). The recent TLGS, however, observed a 24% reduced risk of CKD for high (>6.67 servings/week) vs low intake (<1.98 servings/week) of full-fat dairy, but no association for low-fat dairy (9). The associations for full-fat dairy could be attributed to considerable amounts of conjugated linoleic acid and whey protein present in full-fat dairy, as argued in the paper written by Gaeini et al. (9). Other explanations could be that full-fat dairy products induce higher satiety compared to low-fat dairy products, resulting in lower consumption. Additionally, full-fat dairy products are typically unprocessed, while low-fat

dairy products are often processed and potentially sweetened more frequently. In another study of the Alpha Omega Cohort, biomarkers of dairy and fibre (i.e., C15:0 and C17:0) were also not associated with kidney function decline (37, 38). Dairy is a heterogeneous group of liquid and (semi)solid products that differ in levels of nutrients (e.g. salt, SFAs, probiotics), with potentially different effects on cardiometabolic health. Differences in amount of dairy protein may also play a role, as higher protein intake has been associated with CKD progression (31). However, previous studies, including one in Alpha Omega Cohort (39), found no association between protein from dairy and kidney function decline (33, 40). Finally, differences between our findings for specific dairy groups and those for total dairy may be attributed to differences in the amount and variation of dairy intake in different studies.

Strengths and limitations

Strengths of this analysis include the relatively large cohort of stable post-MI patients with detailed data on potential confounders, including a validated FFQ with high reproducibility for milk, yoghurt and cheese. Limitations include that, although we adjusted for a wide range of dietary and lifestyle confounders, residual confounding cannot be ruled out. Considering kidney function, we lacked 24h-urine samples for measurement of e.g. albuminuria, and GFR was not directly measured. However, our study used the latest 2021 creatinine-cystatin C-based CKD-EPI equation to obtain estimates of GFR, which is considered a valid measure of kidney function (24). Finally, patients who died (n=233) during follow-up were not eligible for this analysis, and we cannot rule out a differential association between dairy and kidney function in this subgroup. However, in a previous Alpha Omega Cohort analysis, dairy products were not associated with (CVD) mortality risk, except for yoghurt, for which a beneficial association was found (19).

Conclusion

To conclude, our results suggest that dairy products may not delay kidney function decline after MI. Results for yoghurt should be interpreted with caution. Evaluation of these findings in other cohorts of CHD patients is warranted, before results can be translated to dietary recommendations in CHD patients.

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Conflict of interest

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

Author contribution

ACvW: conceptualisation, methodology, software, formal analysis, investigation, writing – original draft, visualisation **EC:** methodology, writing-review & editing **TV:** writing-review & editing **JMG:** writing-review & editing.

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Supplemental Table 1 Classification of dairy foods in the Alpha Omega Cohort.

Dairy products	Dairy foods included
Total milk	Skimmed milk, semi-skimmed milk, full-fat milk, and milk in coffee
Low-fat milk	<2% fat milk (skimmed and semi-skimmed milk)
Hard cheeses	Dutch regular 20+ (Swiss sprinkled cheese) 30+, 40+ (Edammer), 45+(Maasdammer), 48+ (Goudse cheese, Amsterdammer, raw milk cheese), 50+ cheese, Parmesan, Gruyère, Emmental, Cheddar, smoked cheese
Total yoghurt	Skimmed plain yoghurt, semi-skimmed plain yoghurt, full-fat plain yoghurt
Low-fat yoghurt	Skimmed and semi-skimmed plain yoghurt
Dairy-based desserts	All sorts of yoghurt with fruits, quark with fruits, chocolate milk, custard, pudding, and porridge

Supplemental Table 2 Baseline dietary intake of 2169 patients of the Alpha Omega Cohort, overall, and by categories of total milk consumption.

		Energy-adjusted total milk consumption (grams/day)		
	Total population (n=2169)	<25 (n=822)	≥25-125 (n=667)	≥125 (n=680)
Energy-adjusted dairy intakes[a], g/d				
Total milk	63.7 [1.0, 141.5]	-9.44 [-28.65, 5.87]	76.0 [47.2, 102.3]	197 [146, 348]
Low-fat milk	38.1 [-15.0, 126]	-19.0 [-34.9, -5.1]	62.8 [30.9, 92.4]	172 [131, 338]
Hard cheese	19.5 [12.3, 32.1]	19.0 [11.2, 31.0]	21.0 [13.7, 34.6]	19.2 [12.0, 30.9]
Total yoghurt	17.9 [-11.7, 63.3]	17.5 [-12.2, 63.2]	18.9 [-9.6, 59.9]	17.5 [-13.7, 68.2]
Low-fat yoghurt	6.97 [-23.53, 59.11]	4.25 [-24.32, 56.96]	10.5 [-21.7, 56.1]	6.60 [-24.11, 64.30]
Dairy desserts	70.0 [47.5, 97.5]	70.4 [46.5, 96.6]	69.6 [49.9, 96.9]	70.0 [47.1, 99.1]
Other dietary intakes				
Alcohol consumption[b], n (%)				
Abstainers	92 (4.2)	31 (3.8)	31 (4.6)	30 (4.4)
Low	1127 (52.0)	381 (46.4)	348 (52.2)	398 (58.5)
Moderate	586 (27.0)	244 (29.7)	173 (25.9)	169 (24.9)
High	364 (16.8)	166 (20.2)	115 (17.2)	83 (12.2)
Whole grains, g/d	120 [87.5, 160]	123 [87.5, 160]	120 [87.5, 161]	118 [87.5, 158]
Refined grains, g/d	38.0 [19.8, 70.0]	40.0 [21.0, 75.3]	37.0 [19.8, 67.8]	36.1 [18.2, 65.8]
Fruits, g/d	110 [43.0, 248]	110 [41.5, 257]	109 [45.0, 240]	113.0 [44.0, 244]
Vegetables, g/d	78.6 [58.2, 103]	79.4 [59.4, 105]	79.5 [59.0, 105]	76.9 [55.2, 98.8]
Red- and processed meat, g/d	70.2 ± 35.5	73.3 ± 36.1	66.9 ± 34.9	69.8 ± 35.0
Sugar sweetened beverages, g/d	28.0 [0.00, 107]	25.2 [0.00, 107]	38.5 [0.00, 109]	21.0 [0.00, 79.4]
Total coffee consumption, g/d	375 [375, 563]	375 [375, 587]	375 [375, 563]	375 [375, 563]
Total tea consumption, g/d	150 [45.0, 450]	375 [54.0, 450]	150 [54.0, 450]	150 [20.1, 450]
Fish consumption, n (%)	1765 (81.4)	658 (80.0)	548 (82.2)	559 (82.2)
Sodium[c], mg/d	2222 ± 659	2292 ± 668	2149 ± 640	2210 ± 660
Total energy intake, kcal/d	1924 ± 517	1990 ± 507	1867 ± 535	1900 ± 503

Values are mean ± standard deviation for normally distributed variables, medians [interquartile range] for skewed variables or n (%) for categorical variables. [a] Classification of dairy foods can be found in Supplemental Table 1. [b] Abstainers: 0 grams/day; low: >0–10 grams/day; moderate: >10–30 grams/day for men or >10–20 grams/day for women, and high: >30 grams/day for men or >20 grams/day for women. [c] Sodium intake was only estimated from foods, since discretionary salt use could not be assessed by the food frequency questionnaire.

Supplemental Table 3 Associations of energy-adjusted dairy subtypes with annual $eGFR_{cr\text{-}cysC}$ change in 1752 male patients of the Alpha Omega Cohort.

	Energy-adjusted categories of dairy consumption, grams/day			
	Low	Intermediate	High	P_{trend} [a]
Total milk	<25 (n=688)	≥25-125 (n=524)	≥125 (n=540)	
Mean ± SD annual $eGFR_{cr\text{-}cysC}$ change, mL/min per 1.73 m^2	-1.56±3.79	-1.78±3.58	-1.73±3.50	
Model 3[b]	Ref	-0.19 (-0.60;0.22)[c]	-0.18 (-0.59;0.24)	0.38
Low-fat milk	<25 (n=811)	≥25-125 (n=508)	≥125 (n=433)	
Mean ± SD annual $eGFR_{cr\text{-}cysC}$ change, mL/min per 1.73 m^2	-1.63±3.71	-1.80±3.61	-1.64±3.54	
Model 3	Ref	-0.19 (-0.59;0.22)	-0.04 (-0.47;0.38)	0.73
Hard cheese	<15 (n=635)	≥15-30 (n=628)	>30 (n=489)	
Mean ± SD annual $eGFR_{cr\text{-}cysC}$ change, mL/min per 1.73 m^2	-1.75±3.59	-1.55±3.72	-1.75±3.60	
Model 3	Ref	0.27 (-0.14;0.68)	-0.10 (-0.55;0.35)	0.79
Total yoghurt	<10 (n=786)	≥10-60 (n=515)	≥60 (n=451)	
Mean ± SD annual $eGFR_{cr\text{-}cysC}$ change, mL/min per 1.73 m^2	-1.45±3.55	-1.85±3.69	-1.88±3.72	
Model 3	Ref	-0.51 (-0.92;-0.10)	-0.53 (-0.96;-0.10)	0.01
Low-fat yoghurt	<10 (n=938)	≥10-60 (n=407)	≥60 (n=407)	
Mean ± SD annual $eGFR_{cr\text{-}cysC}$ change, mL/min per 1.73 m^2	-1.47±3.49	-1.91±3.81	-1.92±3.77	
Model 3	Ref	-0.55 (-0.98;-0.13)	-0.53 (-0.96;-0.10)	0.01
Dairy desserts	<50 (n=543)	≥50-100 (n=829)	≥100 (n=380)	
Mean ± SD annual $eGFR_{cr\text{-}cysC}$ change, mL/min per 1.73 m^2	-1.38±3.66	-1.89±3.66	-1.65±3.53	
Model 3	Ref	-0.59 (-0.99;-0.18)	-0.32 (-0.82;0.17)	0.12

[a] P_{trend} was assessed by treating the categorical variable as a continuous variable in the model. [b] Adjusted for age, total energy intake, smoking status, physical activity, education, alcohol consumption, obesity, renin-angiotensin-aldosterone system blocking drugs, dietary intakes of whole grains, refined grains, fruits, vegetables, red- and processed meat, sugar sweetened beverages, coffee, tea, salt from foods, and fish. [c] β (95% confidence interval) obtained from multivariable linear regression models (all such values). $eGFR_{cr\text{-}cysC}$, estimated glomerular filtration rate based on creatinine and cystatin C; SD, standard deviation.

Supplemental Table 4 Associations of energy-adjusted dairy subtypes with annual $eGFR_{cr\text{-}cysC}$ change in 1775 patients of the Alpha Omega Cohort without diabetes.

	Energy-adjusted categories of dairy consumption, grams/day			
	Low	Intermediate	High	P_{trend} [a]
Total milk	<25 (n=686)	≥25-125 (n=539)	≥125 (n=550)	
Mean ± SD annual $eGFR_{cr\text{-}cysC}$ change, mL/min per 1.73 m^2	-1.37 ± 3.86	-1.77 ± 3.65	-1.57 ± 3.66	
Model 3[b]	Ref	-0.35 (-0.77;0.08)[c]	-0.21 (-0.63;0.21)	0.30
Low-fat milk	<25 (n=823)	≥25-125 (n=508)	≥125 (n=444)	
Mean ± SD annual $eGFR_{cr\text{-}cysC}$ change, mL/min per 1.73 m^2	-1.39 ± 3.84	-1.81 ± 3.62	-1.56 ± 3.68	
Model 3	Ref	-0.45 (-0.86;-0.03)	-0.22 (-0.66;0.21)	0.19
Hard cheese	<15 (n=616)	≥15-30 (n=676)	>30 (n=483)	
Mean ± SD annual $eGFR_{cr\text{-}cysC}$ change, mL/min per 1.73 m^2	-1.53 ± 3.63	-1.67 ± 3.86	-1.42 ± 3.71	
Model 3	Ref	-0.03 (-0.46;0.39)	0.06 (-0.41;0.53)	0.83
Total yoghurt	<10 (n=757)	≥10-60 (n=547)	≥60 (n=471)	
Mean ± SD annual $eGFR_{cr\text{-}cysC}$ change, mL/min per 1.73 m^2	-1.33 ± 3.68	-1.78 ± 3.79	-1.65 ± 3.77	
Model 3	Ref	-0.53 (-0.95;-0.12)	-0.42 (-0.86;0.03)	0.04
Low-fat yoghurt	<10 (n=923)	≥10-60 (n=434)	≥60 (n=418)	
Mean ± SD annual $eGFR_{cr\text{-}cysC}$ change, mL/min per 1.73 m^2	-1.34 ± 3.65	-1.88 ± 3.85	-1.68 ± 3.81	
Model 3	Ref	-0.60 (-1.03;-0.17)	-0.41 (-0.85;0.03)	0.03
Dairy desserts	<50 (n=497)	≥50-100 (n=866)	≥100 (n=412)	
Mean ± SD annual $eGFR_{cr\text{-}cysC}$ change, mL/min per 1.73 m^2	-1.31 ± 3.77	-1.73 ± 3.74	-1.48 ± 3.70	
Model 3	Ref	-0.42 (-0.85;0.01)	-0.26 (-0.77;0.26)	0.29

[a] P_{trend} was assessed by treating the categorical variable as a continuous variable in the model. [b] Adjusted for age, sex, total energy intake, smoking status, physical activity, education, alcohol consumption, obesity, renin-angiotensin-aldosterone system blocking drugs, dietary intakes of whole grains, refined grains, fruits, vegetables, red- and processed meat, sugar sweetened beverages, coffee, tea, salt from foods, and fish. [c] β (95% confidence interval) obtained from multivariable linear regression models (all such values). $eGFR_{cr\text{-}cysC}$, estimated glomerular filtration rate based on creatinine and cystatin C; SD, standard deviation.

Supplemental Table 5 Associations of energy-adjusted dairy subtypes with annual $eGFR_{cr\text{-}cysC}$ change in 1896 patients of the Alpha Omega Cohort without CKD.

	Energy-adjusted categories of dairy consumption, grams/day			
	Low	Intermediate	High	P_{trend} [a]
Total milk	<25 (n=723)	≥25-125 (n=574)	≥125 (n=599)	
Mean ± SD annual $eGFR_{cr\text{-}cysC}$ change, mL/min per 1.73 m^2	-1.75 ± 3.96	-2.03 ± 3.70	-2.00 ± 3.70	
Model 3[b]	Ref	-0.22 (-0.63;0.20)[c]	-0.22 (-0.63;0.20)	0.29
Low-fat milk	<25 (n=867)	≥25-125 (n=540)	≥125 (n=489)	
Mean ± SD annual $eGFR_{cr\text{-}cysC}$ change, mL/min per 1.73 m^2	-1.83 ± 3.93	-1.99 ± 3.63	-1.98 ± 3.77	
Model 3	Ref	-0.14 (-0.55;0.26)	-0.13 (-0.56;0.29)	0.49
Hard cheese	<15 (n=648)	≥15-30 (n=719)	>30 (n=529)	
Mean ± SD annual $eGFR_{cr\text{-}cysC}$ change, mL/min per 1.73 m^2	-1.87 ± 3.66	-1.95 ± 3.97	-1.92 ± 3.74	
Model 3	Ref	0.08 (-0.33;0.50)	0.00 (-0.46;0.45)	0.98
Total yoghurt	<10 (n=805)	≥10-60 (n=568)	≥60 (n=523)	
Mean ± SD annual $eGFR_{cr\text{-}cysC}$ change, mL/min per 1.73 m^2	-1.59 ± 3.67	-2.17 ± 3.86	-2.14 ± 3.90	
Model 3	Ref	-0.61 (-1.02;-0.20)	-0.52 (-0.95;-0.10)	0.01
Low-fat yoghurt	<10 (n=972)	≥10-60 (n=451)	≥60 (n=473)	
Mean ± SD annual $eGFR_{cr\text{-}cysC}$ change, mL/min per 1.73 m^2	-1.64 ± 3.66	-2.23 ± 3.91	-2.17 ± 3.95	
Model 3	Ref	-0.62 (-1.05;-0.20)	-0.49 (-0.92;-0.07)	0.01
Dairy desserts	<50 (n=536)	≥50-100 (n=925)	≥100 (n=435)	
Mean ± SD annual $eGFR_{cr\text{-}cysC}$ change, mL/min per 1.73 m^2	-1.62 ± 3.75	-2.14 ± 3.88	-1.80 ± 3.66	
Model 3	Ref	-0.47 (-0.89;-0.04)	-0.17 (-0.67;0.34)	0.44

[a] P_{trend} was assessed by treating the categorical variable as a continuous variable in the model. [b] Adjusted for age, sex, total energy intake, smoking status, physical activity, education, alcohol consumption, obesity, renin-angiotensin-aldosterone system blocking drugs, dietary intakes of whole grains, refined grains, fruits, vegetables, red- and processed meat, sugar sweetened beverages, coffee, tea, salt from foods, and fish. [c] β (95% confidence interval) obtained from multivariable linear regression models (all such values). $eGFR_{cr\text{-}cysC}$, estimated glomerular filtration rate based on creatinine and cystatin C; CKD, chronic kidney disease; SD, standard deviation.

Supplemental Table 6 Associations of energy-adjusted dairy subtypes with annual $eGFR_{cr\text{-}cysC}$ change in 1686 patients of the Alpha Omega Cohort without obesity.

	Energy-adjusted categories of dairy consumption, grams/day			
	Low	Intermediate	High	P_{trend} [a]
Total milk	<25 (n=659)	≥25-125 (n=513)	≥125 (n=514)	
Mean ± SD annual $eGFR_{cr\text{-}cysC}$ change, mL/min per 1.73 m^2	-1.54 ± 3.91	-1.69 ± 3.79	-1.72 ± 3.74	
Model 3[b]	Ref	-0.08 (-0.53;0.36)[c]	-0.19 (-0.63;0.25)	0.40
Low-fat milk	<25 (n=783)	≥25-125 (n=485)	≥125 (n=418)	
Mean ± SD annual $eGFR_{cr\text{-}cysC}$ change, mL/min per 1.73 m^2	-1.56 ± 3.86	-1.72 ± 3.83	-1.69 ± 3.74	
Model 3	Ref	-0.13 (-0.57;0.30)	-0.16 (-0.61;0.30)	0.47
Hard cheese	<15 (n=592)	≥15-30 (n=642)	>30 (n=452)	
Mean ± SD annual $eGFR_{cr\text{-}cysC}$ change, mL/min per 1.73 m^2	-1.62 ± 3.68	-1.68 ± 3.94	-1.60 ± 3.83	
Model 3	Ref	0.04 (-0.40;0.48)	-0.09 (-0.59;0.40)	0.74
Total yoghurt	<10 (n=740)	≥10-60 (n=499)	≥60 (n=447)	
Mean ± SD annual $eGFR_{cr\text{-}cysC}$ change, mL/min per 1.73 m^2	-1.38 ± 3.78	-1.93 ± 3.84	-1.75 ± 3.84	
Model 3	Ref	-0.65 (-1.09;-0.21)	-0.44 (-0.89;0.02)	0.03
Low-fat yoghurt	<10 (n=891)	≥10-60 (n=393)	≥60 (n=402)	
Mean ± SD annual $eGFR_{cr\text{-}cysC}$ change, mL/min per 1.73 m^2	-1.40 ± 3.73	-2.01 ± 3.98	-1.81 ± 3.84	
Model 3	Ref	-0.68 (-1.14;-0.22)	-0.44 (-0.90;0.02)	0.02
Dairy desserts	<50 (n=488)	≥50-100 (n=816)	≥100 (n=382)	
Mean ± SD annual $eGFR_{cr\text{-}cysC}$ change, mL/min per 1.73 m^2	-1.35 ± 3.81	-1.85 ± 3.91	-1.57 ± 3.62	
Model 3	Ref	-0.51 (-0.95;-0.06)	-0.33 (-0.86;0.20)	0.18

[a] P_{trend} was assessed by treating the categorical variable as a continuous variable in the model. [b] Adjusted for age, sex, total energy intake, smoking status, physical activity, education, alcohol consumption, renin-angiotensin-aldosterone system blocking drugs, dietary intakes of whole grains, refined grains, fruits, vegetables, red- and processed meat, sugar sweetened beverages, coffee, tea, salt from foods, and fish. [c] β (95% confidence interval) obtained from multivariable linear regression models (all such values). $eGFR_{cr\text{-}cysC}$, estimated glomerular filtration rate based on creatinine and cystatin C; SD, standard deviation.

Supplemental Table 7 Associations of energy-adjusted dairy subtypes with annual $eGFR_{cr\text{-}cysC}$ change in 2169 patients of the Alpha Omega Cohort, with and without additional adjustment for other dairy subtypes, for CVD risk factors, and for baseline $eGFR_{cr\text{-}cysC}$.

	Energy-adjusted categories of dairy consumption, grams/day			
	Low	Intermediate	High	P_{trend} [a]
Total milk	<25 (n=822)	≥25-125 (n=667)	≥125 (n=660)	
Model 3[b]	Ref	-0.14 (-0.53;0.26)[c]	-0.21 (-0.60;0.19)	0.30
Model 3 plus adjusted for other dairy subtypes	Ref	-0.19 (-0.59;0.21)	-0.26 (-0.65;0.14)	0.20
Model 3 plus adjusted for CVD risk factors[d]	Ref	-0.14 (-0.53;0.26)	-0.21 (-0.60;0.19)	0.30
Model 3 plus adjusted for baseline $eGFR_{cr\text{-}cysC}$	Ref	-0.03 (-0.41;0.34)	-0.06 (-0.43;0.32)	0.77
Low-fat milk	<25 (n=993)	≥25-125 (n=622)	≥125 (n=554)	
Model 3	Ref	-0.12 (-0.51;0.26)	-0.20 (-0.60;0.21)	0.32
Model 3 plus adjusted for other dairy subtypes	Ref	-0.20 (-0.59;0.19)	-0.27 (-0.68;0.14)	0.17
Model 3 plus adjusted for CVD risk factors	Ref	-0.12 (-0.50;0.27)	-0.20 (-0.60;0.21)	0.33
Model 3 plus adjusted for baseline $eGFR_{cr\text{-}cysC}$	Ref	-0.03 (-0.40;0.34)	-0.03 (-0.41;0.35)	0.87
Hard cheese	<15 (n=737)	≥15-30 (n=837)	>30 (n=595)	
Model 3	Ref	0.00 (-0.40;0.39)	-0.08 (-0.52;0.36)	0.73
Model 3 plus adjusted for other dairy subtypes	Ref	0.00 (-0.39;0.39)	-0.11 (-0.55;0.33)	0.65
Model 3 plus adjusted for CVD risk factors	Ref	0.00 (-0.39;0.40)	-0.08 (-0.51;0.36)	0.75
Model 3 plus adjusted for baseline $eGFR_{cr\text{-}cysC}$	Ref	-0.03 (-0.40;0.34)	-0.01 (-0.43;0.41)	0.95
Total yoghurt	<10 (n=931)	≥10-60 (n=645)	≥60 (n=593)	
Model 3	Ref	-0.60 (-0.99;-0.21)	-0.50 (-0.91;-0.09)	0.01
Model 3 plus adjusted for other dairy subtypes	Ref	-0.56 (-0.96;-0.16)	-0.43 (-0.86;0.00)	0.03
Model 3 plus adjusted for CVD risk factors	Ref	-0.60 (-0.99;-0.21)	-0.50 (-0.90;-0.09)	0.01
Model 3 plus adjusted for baseline $eGFR_{cr\text{-}cysC}$	Ref	-0.53 (-0.90;-0.16)	-0.37 (-0.76;0.02)	0.03
Low-fat yoghurt	<10 (n=1122)	≥10-60 (n=513)	≥60 (n=534)	
Model 3	Ref	-0.58 (-0.99;-0.18)	-0.50 (-0.90;-0.09)	0.01
Model 3 plus adjusted for other dairy subtypes	Ref	-0.55 (-0.96;-0.13)	-0.44 (-0.89;0.01)	0.03
Model 3 plus adjusted for CVD risk factors	Ref	-0.58 (-0.99;-0.18)	-0.49 (-0.90;-0.09)	0.01
Model 3 plus adjusted for baseline $eGFR_{cr\text{-}cysC}$	Ref	-0.49 (-0.88;-0.11)	-0.35 (-0.74;0.03)	0.04

Supplemental Table 7 continued

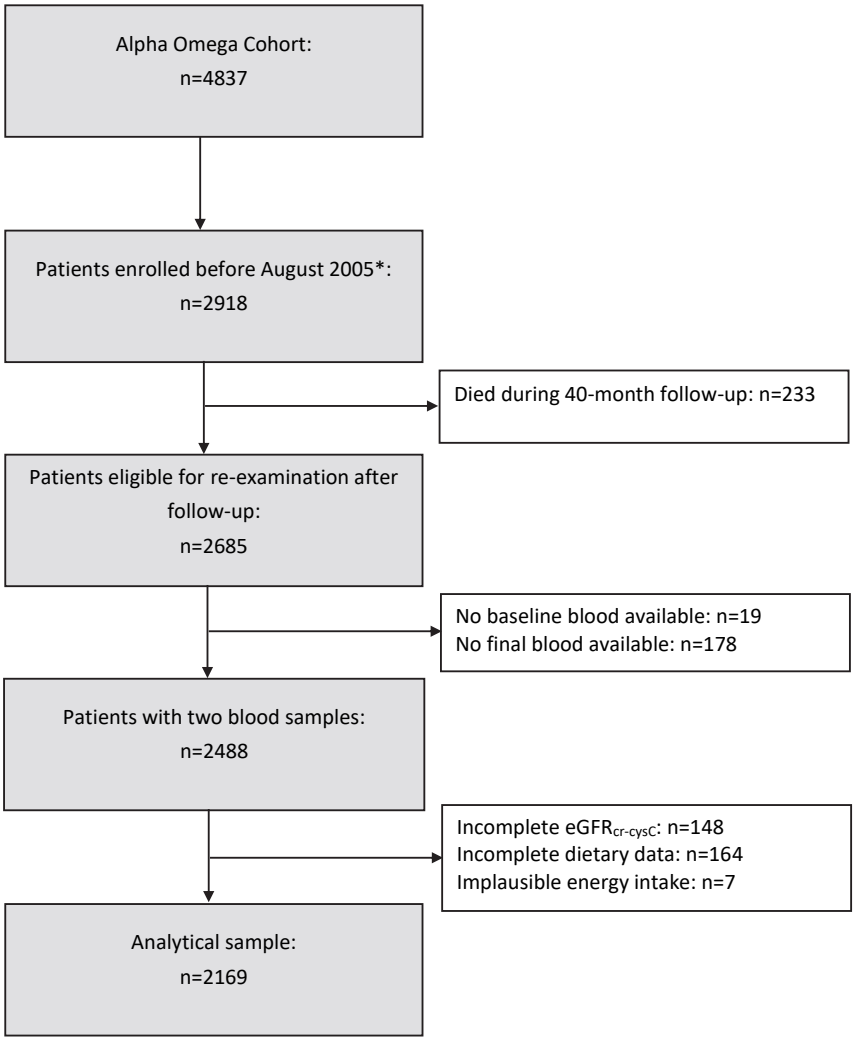
	Energy-adjusted categories of dairy consumption, grams/day			
	Low	Intermediate	High	P_{trend} [a]
Dairy desserts	<50 (n=603)	≥50-100 (n=1064)	≥100 (n=502)	
Model 3	Ref	-0.46 (-0.87;-0.06)	-0.24 (-0.72;0.24)	0.28
Model 3 plus adjusted for other dairy subtypes	Ref	-0.42 (-0.83;-0.01)	-0.20 (-0.69;0.29)	0.41
Model 3 plus adjusted for CVD risk factors	Ref	-0.47 (-0.87;-0.06)	-0.24 (-0.72;0.24)	0.29
Model 3 plus adjusted for baseline $eGFR_{cr\text{-}cysC}$	Ref	-0.42 (-0.80;-0.04)	-0.20 (-0.65;0.26)	0.35

[a] P_{trend} was assessed by treating the categorical variable as a continuous variable in the model. [b] Adjusted for age, sex, total energy intake, smoking status, physical activity, education, alcohol consumption, obesity, renin-angiotensin-aldosterone system blocking drugs, dietary intakes of whole grains, refined grains, fruits, vegetables, red- and processed meat, sugar sweetened beverages, coffee, tea, salt from foods, and fish. [c] β (95% confidence interval) obtained from multivariable linear regression models (all such values). [d] Adjusted for triglycerides, total serum cholesterol, and hypertension. $eGFR_{cr\text{-}cysC}$, estimated glomerular filtration rate based on creatinine and cystatin C; CVD, cardiovascular disease.

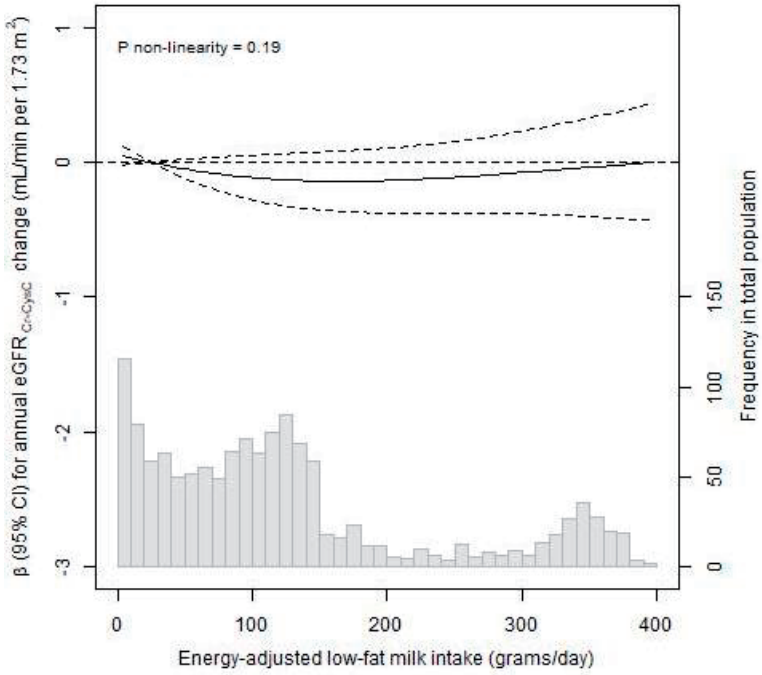
Supplemental Table 8 Associations of energy-adjusted dairy subtypes with annual $eGFR_{cysC}$ change in 2247 patients of the Alpha Omega Cohort.

	Energy-adjusted categories of dairy consumption, grams/day			
	Low	Intermediate	High	P_{trend} [a]
Total milk	<25 (n=840)	≥25-125 (n=692)	≥125 (n=715)	
Mean ± SD annual $eGFR_{cysC}$ change, mL/min per 1.73 m^2	-1.01 ± 3.32	-0.99 ± 3.20	-0.96 ± 3.09	
Model 3[b]	Ref	0.02 (-0.30;0.34)[c]	0.02 (-0.30;0.34)	0.91
Low-fat milk	<25 (n=1026)	≥25-125 (n=639)	≥125 (n=582)	
Mean ± SD annual $eGFR_{cysC}$ change, mL/min per 1.73 m^2	-1.04 ± 3.30	-0.94 ± 3.17	-0.96 ± 3.09	
Model 3	Ref	0.09 (-0.22;0.41)	0.03 (-0.30;0.35)	0.81
Hard cheese	<15 (n=766)	≥15-30 (n=873)	>30 (n=608)	
Mean ± SD annual $eGFR_{cysC}$ change, mL/min per 1.73 m^2	-0.99 ± 3.14	-0.98 ± 3.35	-1.01 ± 3.09	
Model 3	Ref	0.05 (-0.27;0.37)	-0.04 (-0.40;0.32)	0.85
Total yoghurt	<10 (n=987)	≥10-60 (n=670)	≥60 (n=590)	
Mean ± SD annual $eGFR_{cysC}$ change, mL/min per 1.73 m^2	-0.84 ± 3.10	-1.19 ± 3.28	-1.02 ± 3.30	
Model 3	Ref	-0.46 (-0.77;-0.14)	-0.27 (-0.61;0.06)	0.06
Low-fat yoghurt	<10 (n=1177)	≥10-60 (n=534)	≥60 (n=536)	
Mean ± SD annual $eGFR_{cysC}$ change, mL/min per 1.73 m^2	-0.84 ± 3.05	-1.32 ± 3.41	-1.00 ± 3.31	
Model 3	Ref	-0.58 (-0.91;-0.25)	-0.24 (-0.57;0.09)	0.05
Dairy desserts	<50 (n=657)	≥50-100 (n=1090)	≥100 (n=500)	
Mean ± SD annual $eGFR_{cysC}$ change, mL/min per 1.73 m^2	-0.78 ± 3.00	-1.14 ± 3.36	-0.94 ± 3.12	
Model 3	Ref	-0.40 (-0.73;-0.08)	-0.26 (-0.64;0.13)	0.15

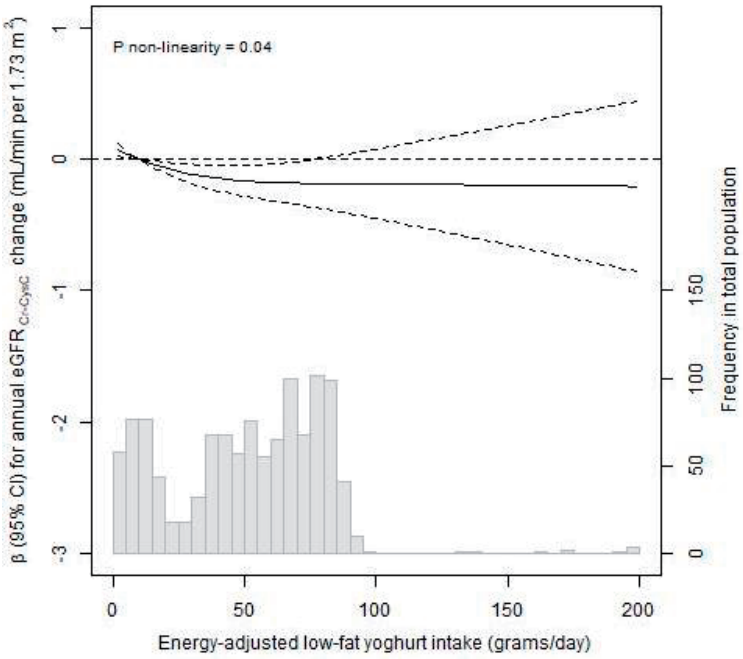
[a] P_{trend} was assessed by treating the categorical variable as a continuous variable in the model. [b] Adjusted for age, sex, total energy intake, smoking status, physical activity, education, alcohol consumption, obesity, renin-angiotensin-aldosterone system blocking drugs, dietary intakes of whole grains, refined grains, fruits, vegetables, red- and processed meat, sugar sweetened beverages, coffee, tea, salt from foods, and fish. [c] β (95% confidence interval) obtained from multivariable linear regression models (all such values). $eGFR_{cysC}$, estimated glomerular filtration rate based on cystatin C; SD, standard deviation.



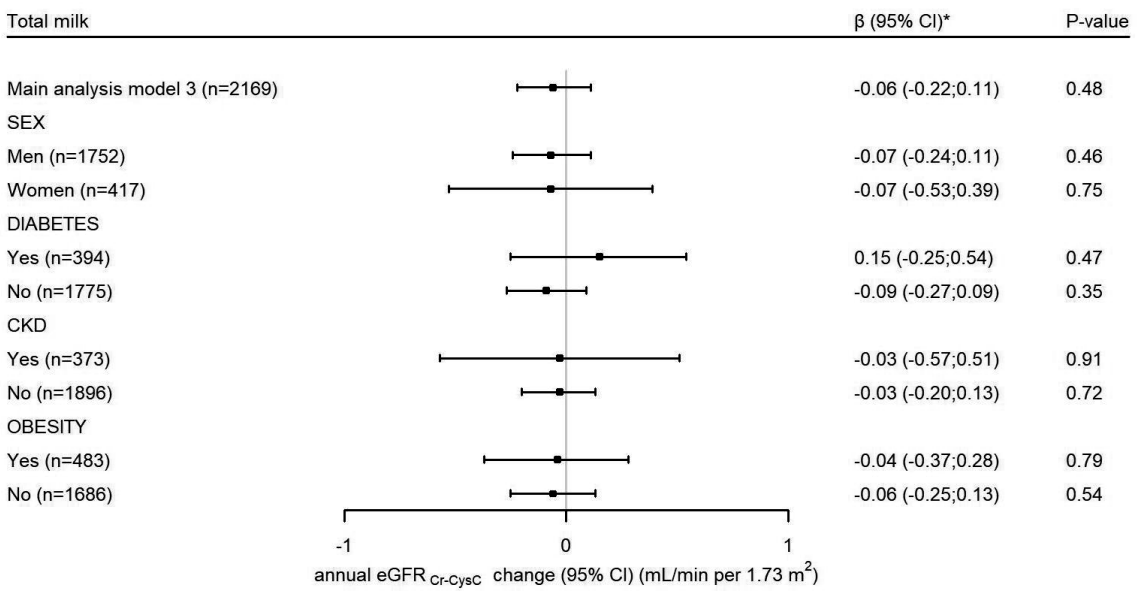
Supplemental Fig. 1 Flowchart for selection of the analytical sample of the Alpha Omega Cohort. *Due to financial constraints, only these patients were eligible for follow-up measurements. $eGFR_{cr\text{-}cysC}$, estimated glomerular filtration rate based on creatinine and cystatin C.



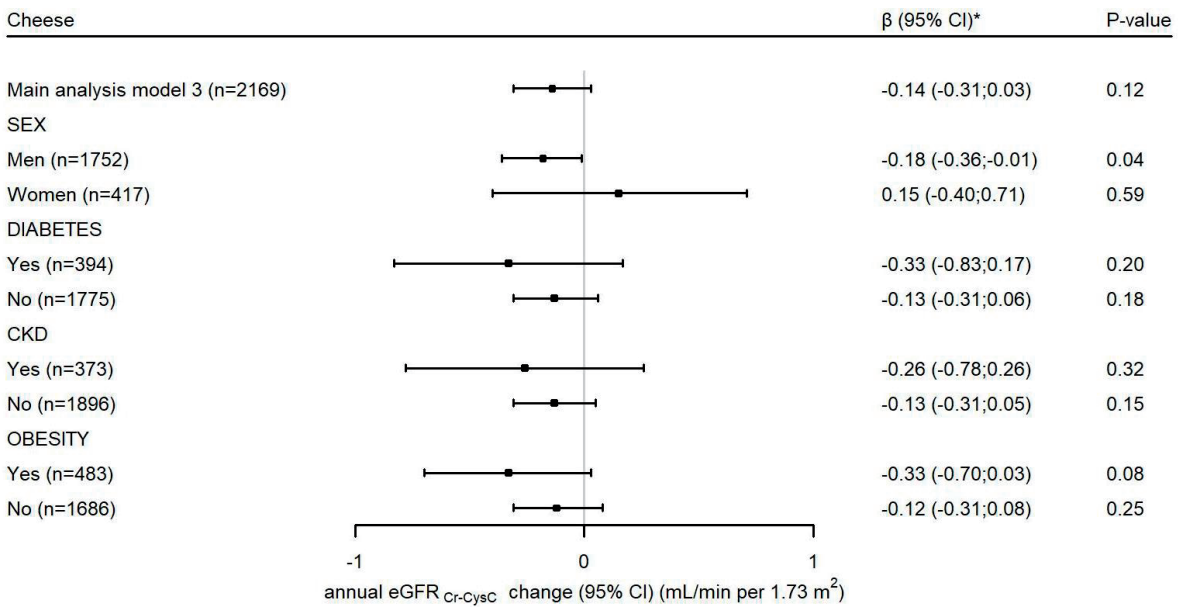
Supplemental Fig. 2 Relationship between intake of energy-adjusted low-fat milk as continuous variable and annual $eGFR_{cr\text{-}cysC}$ change among 2169 patients of the Alpha Omega Cohort. Solid lines represent beta coefficients and dashed lines represent 95% CIs. Negative coefficients indicate more $eGFR_{cr\text{-}cysC}$ decline and positive coefficients indicate less $eGFR_{cr\text{-}cysC}$ decline. Three-knot restricted cubic splines was used, with an energy-adjusted intake of 25 grams/day as reference point. Betas were adjusted for age, sex, total energy intake, smoking status, physical activity, education, alcohol consumption, obesity, renin-angiotensin-aldosterone system blocking drugs, and dietary intake of whole grains, refined grains, fruits, vegetables, red- and processed meat, sugar sweetened beverages, coffee, tea, salt from foods, and fish. $eGFR_{cr\text{-}cysC}$, estimated glomerular filtration rate based on creatinine and cystatin C; CIs, confidence intervals.



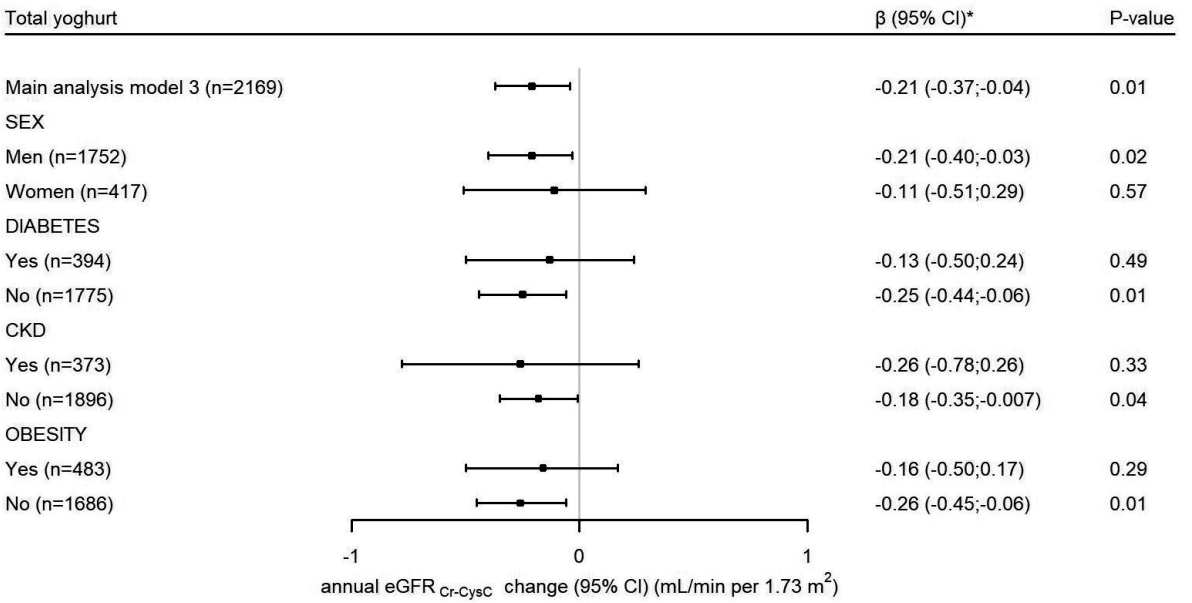
Supplemental Fig. 3 Relationship between intake of energy-adjusted low-fat yoghurt as continuous variable and annual $eGFR_{cr\text{-}cysC}$ change among 2169 patients of the Alpha Omega Cohort. Solid lines represent beta coefficients and dashed lines represent 95% CIs. Negative coefficients indicate more $eGFR_{cr\text{-}cysC}$ decline and positive coefficients indicate less $eGFR_{cr\text{-}cysC}$ decline. Three-knot restricted cubic splines was used, with an energy-adjusted intake of 10 grams/day as reference point. Betas were adjusted for age, sex, total energy intake, smoking status, physical activity, education, alcohol consumption, obesity, renin-angiotensin-aldosterone system blocking drugs, and dietary intake of whole grains, refined grains, fruits, vegetables, red- and processed meat, sugar sweetened beverages, coffee, tea, salt from foods, and fish. $eGFR_{cr\text{-}cysC}$, estimated glomerular filtration rate based on creatinine and cystatin C; CIs, confidence intervals.



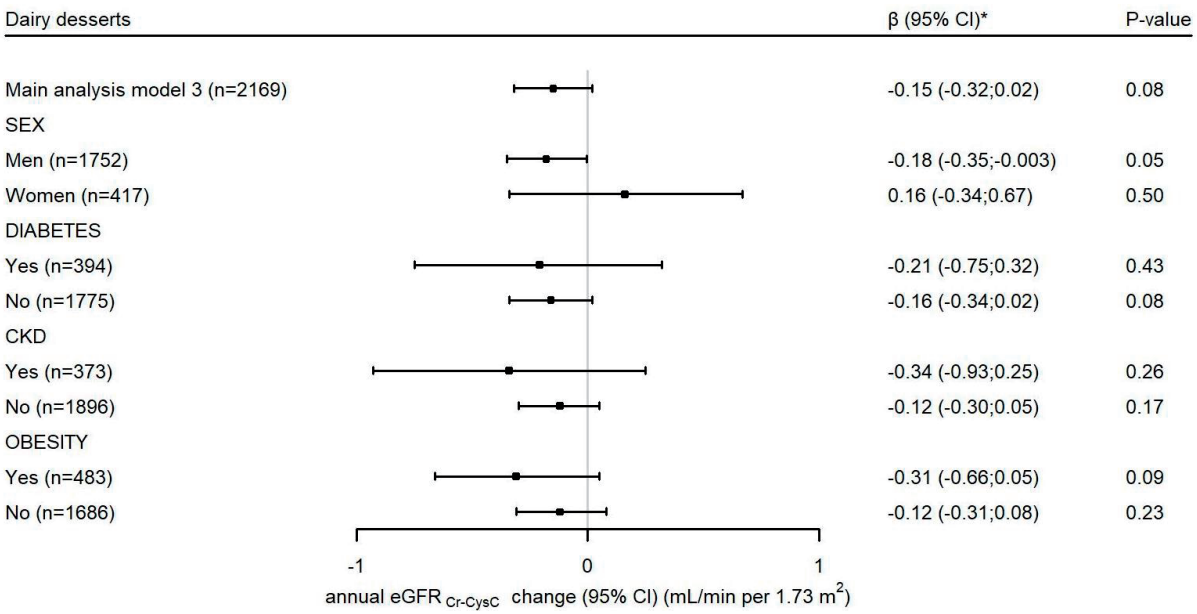
Supplemental Fig. 4 Associations between one standard deviation increment of energy-adjusted total milk and annual $eGFR_{cr\text{-}cysC}$ change in patients of the Alpha Omega Cohort, as well as in subgroups of sex, diabetes, CKD, and obesity. * For each dairy product, betas were adjusted for age, sex (but not when stratified), total energy intake, smoking status, physical activity, education, alcohol consumption, obesity (but not when stratified), renin-angiotensin-aldosterone system blocking drugs, and dietary intake of whole grains, refined grains, fruits, vegetables, red- and processed meat, sugar sweetened beverages, coffee, tea, salt from foods, and fish. $eGFR_{cr\text{-}cysC}$, estimated glomerular filtration rate based on creatinine and cystatin C; CI, confidence interval; CKD, chronic kidney disease.



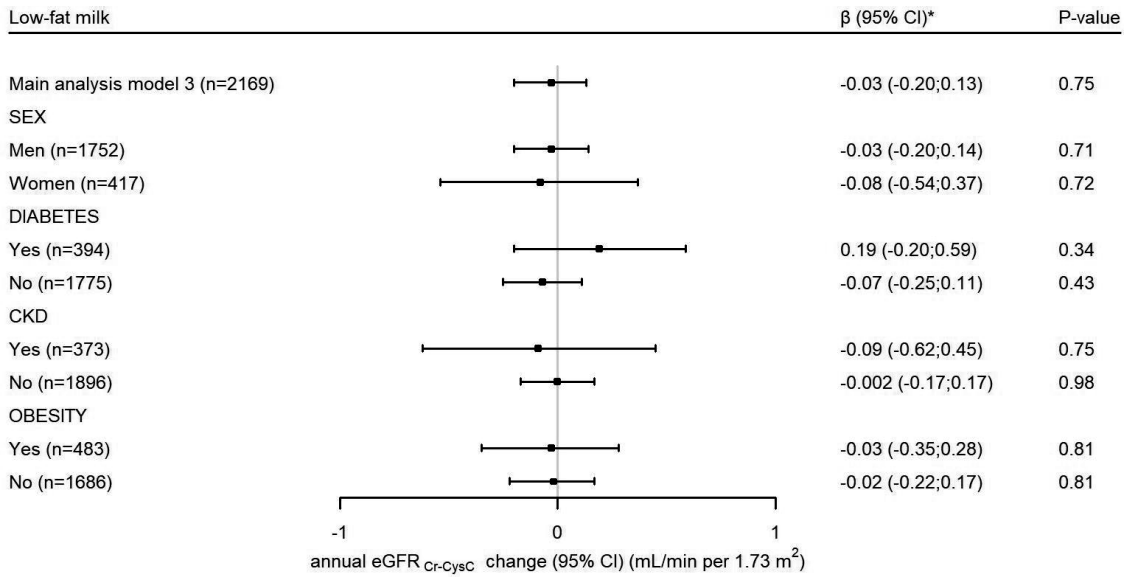
Supplemental Fig. 5 Associations between one standard deviation increment of energy-adjusted cheese and annual $eGFR_{cr\text{-}cysC}$ change in patients of the Alpha Omega Cohort, as well as in subgroups of sex, diabetes, CKD, and obesity. * For each dairy product, betas were adjusted for age, sex (but not when stratified), total energy intake, smoking status, physical activity, education, alcohol consumption, obesity (but not when stratified), renin-angiotensin-aldosterone system blocking drugs, and dietary intake of whole grains, refined grains, fruits, vegetables, red- and processed meat, sugar sweetened beverages, coffee, tea, salt from foods, and fish. $eGFR_{cr\text{-}cysC}$, estimated glomerular filtration rate based on creatinine and cystatin C; CI, confidence interval; CKD, chronic kidney disease.



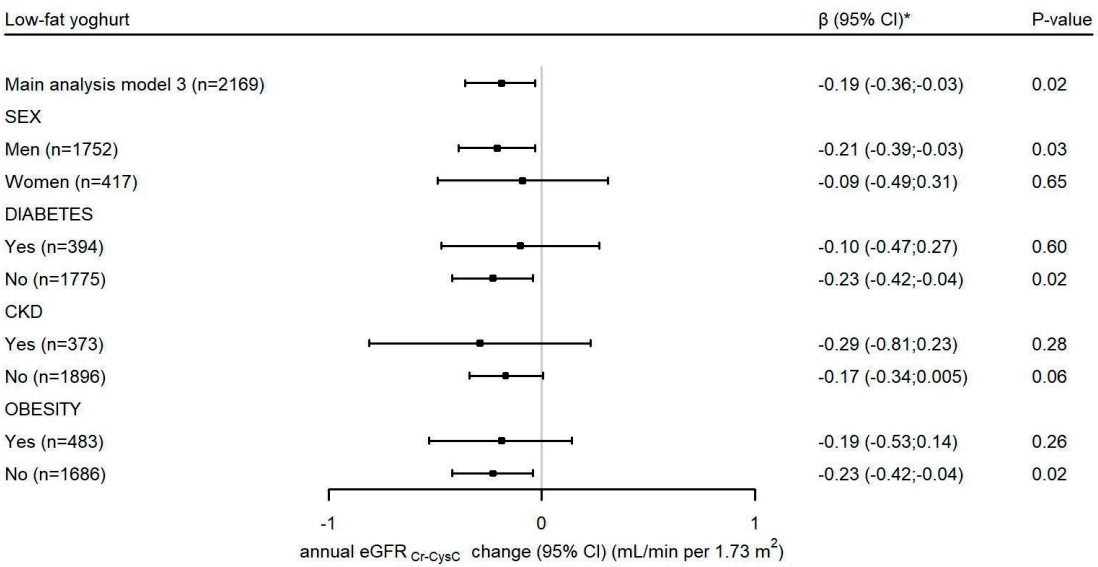
Supplemental Fig. 6 Associations between one standard deviation increment of energy-adjusted total yoghurt and annual $eGFR_{cr\text{-}cysc}$ change in patients of the Alpha Omega Cohort, as well as in subgroups of sex, diabetes, CKD, and obesity. * For each dairy product, betas were adjusted for age, sex (but not when stratified), total energy intake, smoking status, physical activity, education, alcohol consumption, obesity (but not when stratified), renin-angiotensin-aldosterone system blocking drugs, and dietary intake of whole grains, refined grains, fruits, vegetables, red- and processed meat, sugar sweetened beverages, coffee, tea, salt from foods, and fish. $eGFR_{cr\text{-}cysC}$, estimated glomerular filtration rate based on creatinine and cystatin C; CI, confidence interval; CKD, chronic kidney disease.



Supplemental Fig. 7 Associations between one standard deviation increment of energy-adjusted dairy desserts and annual $eGFR_{cr\text{-}cysC}$ change in patients of the Alpha Omega Cohort, as well as in subgroups of sex, diabetes, CKD, and obesity. * For each dairy product, betas were adjusted for age, sex (but not when stratified), total energy intake, smoking status, physical activity, education, alcohol consumption, obesity (but not when stratified), renin-angiotensin-aldosterone system blocking drugs, and dietary intake of whole grains, refined grains, fruits, vegetables, red- and processed meat, sugar sweetened beverages, coffee, tea, salt from foods, and fish. $eGFR_{cr\text{-}cysC}$, estimated glomerular filtration rate based on creatinine and cystatin C; CI, confidence interval; CKD, chronic kidney disease.



Supplemental Fig. 8 Associations between one standard deviation increment of energy-adjusted low-fat milk and annual $eGFR_{cr\text{-}cysc}$ change in patients of the Alpha Omega Cohort, as well as in subgroups of sex, diabetes, CKD, and obesity. *Betas were adjusted for age, sex (but not when stratified), total energy intake, smoking status, physical activity, education, alcohol consumption, obesity (but not when stratified), renin-angiotensin-aldosterone system blocking drugs, and dietary intake of whole grains, refined grains, fruits, vegetables, red- and processed meat, sugar sweetened beverages, coffee, tea, salt from foods, and fish. $eGFR_{cr\text{-}cysC}$, estimated glomerular filtration rate based on creatinine and cystatin C; CI, confidence interval; CKD, chronic kidney disease.



Supplemental Fig. 9 Associations between one standard deviation increment of energy-adjusted low-fat yoghurt and annual $eGFR_{cr\text{-}cysC}$ change in patients of the Alpha Omega Cohort, as well as in subgroups of sex, diabetes, CKD, and obesity. *Betas were adjusted for age, sex (but not when stratified), total energy intake, smoking status, physical activity, education, alcohol consumption, obesity (but not when stratified), renin-angiotensin-aldosterone system blocking drugs, and dietary intake of whole grains, refined grains, fruits, vegetables, red- and processed meat, sugar sweetened beverages, coffee, tea, salt from foods, and fish. $eGFR_{cr\text{-}cysC}$, estimated glomerular filtration rate based on creatinine and cystatin C; CI, confidence interval; CKD, chronic kidney disease.

Part C

Blood biomarkers and kidney function

Chapter 7

Plasma fatty acids and kidney function decline in cardiovascular patients of the Alpha Omega Cohort

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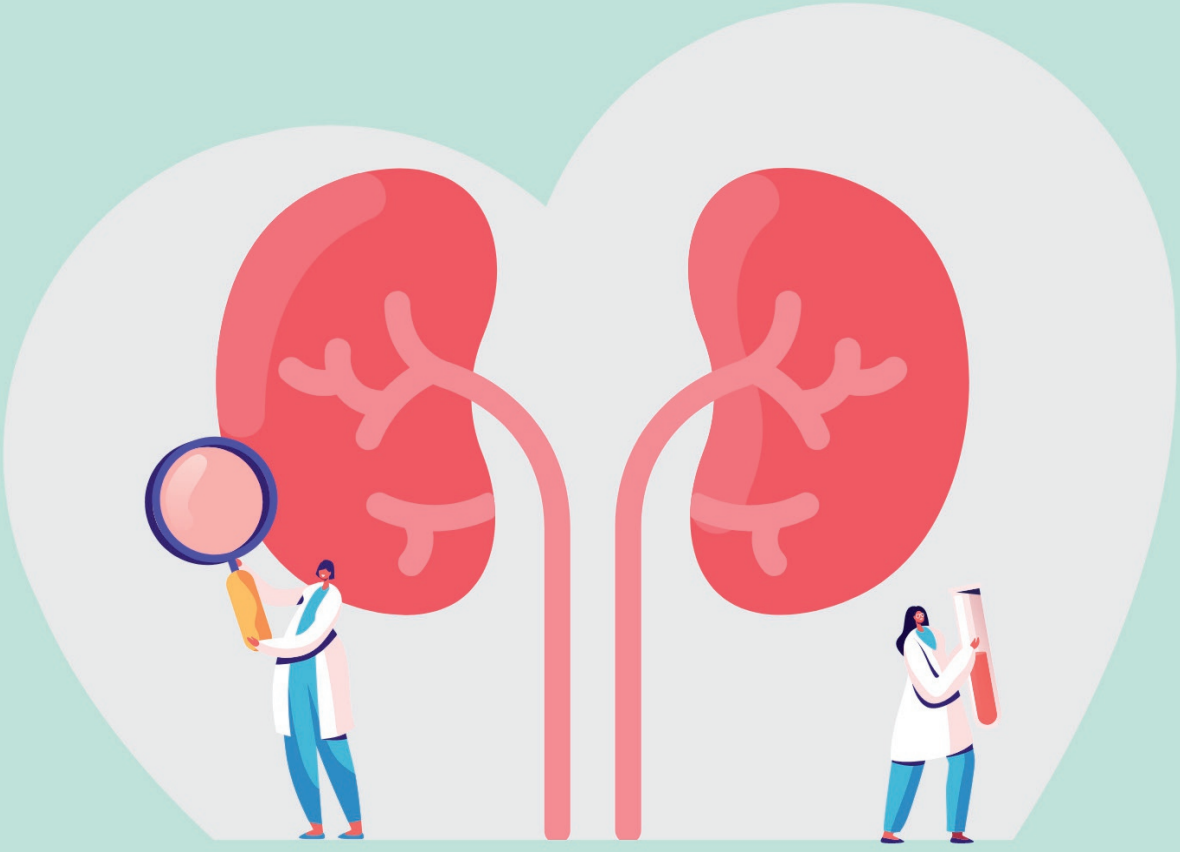

Abstract

Background and aims Age-related kidney function decline is accelerated in patients with coronary heart disease (CHD). CHD and chronic kidney disease may share common etiologies. We examined whether plasma fatty acids (FAs) delay kidney function decline after myocardial infarction (MI).

Methods and results The analysis included 2329 Dutch post-MI patients aged 60-80y (Alpha Omega Cohort) most receiving state-of-the-art medications. Plasma FAs (% total FAs) in cholesteryl esters were assessed at baseline (2002-2006), and ~40 months change in creatinine-cystatin C based glomerular filtration rate was estimated (eGFR, in mL/min per 1.73 m^2). Beta coefficients for annual eGFR change in relation to plasma linoleic acid (LA; 50.1% of total FAs in CE), omega-3 FAs (EPA+DHA; 1.7%), odd-chain FAs (C15:0 and C17:0; 0.2%), and C14:0 (0.7%) were obtained from linear regression analyses adjusted for age, sex, smoking, and alcohol intake. Mean baseline eGFR ± SD was 78.5 ± 18.7, which declined by 4.7 ± 13.1 during follow-up, or 1.4 ± 3.9 per year. The annual decline in eGFR was less in patients with higher plasma LA (adjusted beta: +0.40 for LA >47 vs ≤47%, 95% CI: 0.01;0.78; p=0.046). Associations of plasma LA with annual eGFR decline were stronger in 437 patients with prevalent diabetes (1.21, 0.24;2.19) and in 402 patients with prevalent CKD (eGFR<60; 0.90, -0.09;1.89). Weaker, non-significant associations with kidney function decline were observed for the other plasma FAs.

Conclusion Higher plasma LA may be a good predictor of less kidney function decline after MI, particularly in patients with prevalent diabetes.

Introduction

Chronic kidney disease (CKD) is a major public health problem worldwide. Over the past decades, the number of adults suffering from CKD has increased substantially (1), including a strong increase in (co)morbidity and mortality rates (2, 3). In general, CKD is commonly defined as an estimated glomerular filtration rate (eGFR) <60 mL/min per 1.73 m^2 for at least three consecutive months (4). Kidney function declines after age 40y by approximately 1.0 mL/min per 1.73 m^2 per year (5, 6). After myocardial infarction (MI), however, this process is accelerated (7). In the Alpha Omega Cohort of state-of-the-art drug-treated, Dutch post-MI patients, kidney function decline was adversely associated with (abdominal) obesity, diabetes, high blood pressure, and smoking (8, 9). When compared to patients with eGFR >90 mL/min per 1.73 m^2, a 2-3-fold higher risk of mortality from cardiovascular disease (CVD) or other causes was found in patients with an eGFR of 30-59 mL/min per 1.73 m^2, and an even 4-6-fold higher risk in patients with an eGFR <30 mL/min per 1.73 m^2 (10). As a result, there is a clear need for targeted strategies to delay kidney function decline after MI.

Altered fatty acid (FA) profiles in blood have been observed in patients with CKD (11, 12) and cardiometabolic disease (CMD) (13). In prospective population-based studies, plasma FAs in various lipid compartments, including cholesteryl esters (CE), were associated with cardiometabolic endpoints (14, 15). Neutral or protective associations were found for higher levels of plasma linoleic acid (LA) (14, 16, 17), omega-3 FAs (eicosapentaenoic and docosahexaenoic acid, EPA and DHA) (16, 18, 19), and odd-chain fatty acids (OCFAs, i.e., C15:0 and C17:0) (20-23). C14:0 is less well studied, and its role in CMD remains unclear (22, 24). Overall, population-based data of plasma FA and kidney function decline or CKD are scarce. A prospective cohort study with three years of follow-up showed a smaller decline in creatinine clearance among 676 healthy Italian elderly with higher plasma CE PUFA levels (25). Plasma FAs have been proposed as biomarkers of dietary intake, reflecting PUFAs (plasma LA) (26), fish (plasma EPA+DHA) (19), and dairy (plasma OCFAs and C14:0) (27, 28). Nevertheless, an impaired metabolism may also affect plasma FAs, thereby, attenuating their correlation with diet as was observed for LA in cardiometabolic patients (29). Interestingly, several population-based studies have shown an altered plasma FA composition in the presence of low-grade inflammation (30), insulin resistance (31, 32), and excess abdominal fat (33).

To the best of our knowledge, no studies have been performed on plasma FAs and kidney function decline after MI. As such, we examined the associations between plasma LA, EPA+DHA, OCFAs, and C14:0, measured in CE, and kidney function decline after ~40 months of follow-up in Dutch, post-MI patients from the Alpha Omega Cohort.

Methods

Study design and population

We used data from the Alpha Omega Cohort, a prospective study of 4837 Dutch patients aged 60-80y (78% males) with a verified clinical diagnosis of MI <10y prior to enrolment. Most patients received state-of-the-art medication, such as statins (86%) and antihypertensives (89%) (34). Patients were enrolled between 2002 and 2006 ('baseline') and followed up for cause-specific mortality. During the first ~40 months of follow-up, patients participated in a randomised trial of n-3 FAs versus placebo, which had no effect on recurrence of major cardiovascular events (34, 35). Patients were extensively examined at baseline, which included questionnaires on health, lifestyle, medication, and diet, as well as physical examination by trained research nurses, including blood sampling. Data collection was repeated after ~40 months in patients who had been enrolled until August 2005 (only ~60% of the cohort due to financial constraints). The study was approved by the medical ethics committee at the Haga Hospital (The Hague, The Netherlands), and all patients provided oral and written informed consent.

Patients with blood samples at baseline and after ~40 months were eligible for the present study of plasma FAs and change in eGFR (n=2488). Patients with incomplete data for the assessment of eGFR (n=145), missing data on plasma CE (n=10), and >5% unknown FAs in CE (n=4) were excluded. In total, 2329 patients were available for analyses (**Supplemental Fig. 1**).

Measurement of FAs in plasma CE

Approximately 30 mL of blood was sampled either at the patient's home or at the hospital by trained research nurses with about half of the cohort in a fasting state. Blood was then packaged in sealed envelopes and sent by postal mail to a central laboratory (36). FA composition analysis of LA (C18:2n-6), pentadecanoic acid (C15:0), heptadecanoic acid (C17:0), EPA (C20:5n-3), DHA (C22:6n-3), and myristic acid (C14:0) from 10 mL EDTA blood was performed at the Division of Human Nutrition and Health, Wageningen University, the Netherlands. Detailed laboratory and quality control methods have been described elsewhere (29). In brief, total lipids were first extracted from plasma blood samples and subsequently separated into CE lipid pools using solid phase extraction silica columns (Chrompack, Middelburg, the Netherlands). FAs were trans-esterified into FA methyl esters and analysed by gas chromatography. FAs were identified by comparing retention times with FA standards (Nu-Chek Prep, Elysian, MN) and expressed as weight percentage relative to total FA content (% total FAs). FA analyses in CE took place in different years, which could have affected the stability. Nevertheless, stable FA content was observed over 6-9 years of storage at -80 ℃ by a high intraclass correlation coefficient for LA, EPA, and DHA (r>0.90) (29).

Kidney function assessment

At baseline and after ~40 months of follow-up, serum creatinine (cr) and serum cystatin C (cysC) were measured in stored blood samples in a central laboratory (37, 38). Serum cysC was measured using a particle-enhanced immunonephelometric assay and serum cr was assessed using the modified kinetic Jaffé method as described in detail elsewhere (10). We estimated GFR based on both serum cr and serum cysC Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation from 2012, which takes age, sex, and race into account (38). Change in eGFR was calculated by subtracting each patient's baseline eGFR from their follow-up eGFR with values <0 indicating a deterioration and values >0 an improvement in kidney function over time. Assuming a linear decline over time, we estimated the annual eGFR change: an individual's total change in eGFR was divided by months of follow-up and multiplied by 12. Rapid kidney function decline was defined as an annual eGFR change of ≥3 mL/min per 1.73 m^2 (39).

Other measurements

Information about demographic variables and lifestyle habits was collected through self-administered questionnaires as previously described in detail elsewhere (34). Smoking status was categorised into never, former, and current. BMI was calculated as weight in kilograms divided by the square of height in meters; obesity was defined as BMI ≥ 30 kg/m^2. Habitual dietary intakes were assessed with a 203-item validated food frequency questionnaire (FFQ), which was an extended version of a previous 104-item questionnaire specifically designed to estimate different FAs and cholesterol (40, 41). Alcohol intake was assessed with the FFQ and categorised as no (ethanol intake 0 g/day), low (>0-10 g/day), moderate (women: >10-20 g/day; men: >10-30 g/day), and high (women: >20 g/day; men: >30 g/day).

Systolic and diastolic blood pressure (BP) was measured twice on the left arm in a seated position using an automated device (Omron HEM-711) following a 10-minute rest; and values were averaged. Hypertension was defined as high blood pressure (systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg) or use of antihypertensive drugs. Blood lipids, such as total cholesterol, high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c), and triglycerides (mmol/L), and plasma glucose (mmol/L) were analysed using standardized kits (Hitachi 912, Roche Diagnostics, Basel, Switzerland). Diabetes mellitus was considered present in case of a self-reported physician's diagnosis, use of glucose lowering drugs, or elevated plasma glucose level (≥7.0 mmol/L if fasted for ≥4 h or ≥11.1 mmol/L if not fasted).

CKD was defined as eGFR <60 mL/min per 1.73 m^2 (4). Medication was coded according to the Anatomical Therapeutic Chemical (ATC) Classification System (42): antihypertensive drugs (CO2, C03, C07, C08, and C09), anti-thrombotic drugs (B01), and statins (C10AA and C10B) (34, 35).

Statistical analysis

Normality of the data was checked visually using histograms. Baseline characteristics are presented as mean ± standard deviation (SD) for normally distributed variables, median (interquartile range, IQR) for skewed variables, and frequency (%) for categorical variables.

Multivariable linear regression was used to study the associations between each of the plasma FAs in CE as categorical variable and per SD increase, and annual eGFR change. Plasma LA was divided into quartiles (Q1 as low, Q2-Q4 as high); the median-split of the distribution was used for plasma EPA+DHA, C15:0, C17:0, and C14:0 (below median as low, above median as high). Regression coefficients are presented as unstandardised betas with 95% confidence intervals (CIs). For each FA, two models were created. Model one included age, sex, and total serum cholesterol. Model two additionally included BMI, smoking status (three categories), alcohol intake (four categories), hypertension (two categories), hours of fasting before blood collection, statin use (two categories), and all remaining plasma FAs under study (either LA, EPA+DHA, C15:0, C17:0, C14:0, depending on the exposure). Supplemental intake of low doses of n-3 FAs during the Alpha Omega Trial (35) was not considered a confounder and omitted from the multivariable models given its random assignment in the trial. In multivariable models of annual eGFR change, interaction terms for treatment group with different plasma FAs were not statistically significant ($p>0.20$ for all interaction terms), and therefore no stratification by treatment group was performed. EPA and DHA were combined because they are both highly correlated with fish intake (19). To avoid the risk of biased (inflated) estimates, no adjustment for baseline eGFR was made when analysing eGFR change (43).

Missing data for fasting status (n=96), dietary factors (e.g. alcohol intake, n=166), BMI (n=3), and total serum cholesterol (n=12) were imputed with sex-specific means or medians depending on their distributions. For all FAs, analyses were repeated in subsamples of 437 diabetic and 1892 non-diabetic patients and in subsamples of 402 patients with CKD and 1927 without CKD. Since the metabolic n-3 and n-6 pathways may be intertwined (44), additional subgroup analyses were conducted in patients with low (below median) and high (above median) plasma EPA+DHA (n=1163 vs n=1166, respectively) when analysing plasma LA and in patients with low (below median) and high (above median) plasma LA (n=1164 vs n=1165, respectively) when analysing plasma EPA+DHA. For each of the subgroup analyses, potential effect modification was tested by including interaction terms with each plasma FA under study in model two. Rstudio version 3.6.0 was used for all analyses and a two-sided p-value <0.05 was considered statistically significant.

Results

Patient characteristics

Patients had a median (IQR) age of 69 years (64-73) and 81% were male. Most patients were treated with antithrombotic drugs (98%), antihypertensive drugs (87%), and/or statins (85%). At baseline, 19% of the patients had diabetes and 95% had hypertension. Patients had a BMI of 28 ± 4 kg/m^2 (23% obese), 15% were current smokers, and 16% had a high alcohol intake (>30 g/day for men and >20 g/day for women). Mean ± SD intake of LA was 12 ± 7 g/day (5.7 energy%). Median (IQR) fish intake was 12 (4-17) g/day with 18% of patients consuming no fish; and EPA+DHA intake was 101 (40-176) mg/day. At baseline, patients had an eGFR of 79 ± 19 mL/min per 1.73 m^2 and 17% suffered from CKD (**Table 1**). During an average follow-up period of 41 ± 1.4 months, eGFR declined by 4.74 ± 13.08 mL/min per 1.73 m^2, corresponding to a yearly decline of 1.38 ± 3.79 mL/min per 1.73 m^2 (**Supplemental Fig. 2**).

Table 1 Baseline characteristics of 2329 post-MI patients with plasma cholesteryl esters (CE) of the Alpha Omega Cohort.

	Patients with plasma CE (n=2329)
Age, years	68.6 (64.3-73.2)
Men, n (%)	1877 (80.6)
BMI (kg/m^2)[a]	27.7 ± 3.6
Obesity, n (%)[a,b]	526 (22.6)
Underweight, n (%)[b]	18 (0.8)
Time since MI, years[c]	4.00 (1.96-6.44)
Smoking, n (%)	
Never	388 (16.7)
Former	1582 (67.9)
Current	359 (15.4)
Alcohol intake, n (%)[d,e]	
No	93 (4.0)
Low	1127 (48.4)
Moderate	581 (24.9)
High	362 (15.5)
Medication use, n (%)[f]	
Statins	1985 (85.2)
Antihypertensive drugs	2026 (87.0)
Antithrombotic drugs	2275 (97.7)
Serum lipids, mmol/L[g]	
Total cholesterol	4.84 ± 0.93
LDL cholesterol	2.74 ± 0.80
HDL cholesterol	1.26 ± 0.32
Triglycerides	1.64 (1.22-2.28)
Hours of fasting before blood collection[i]	4.01 (2.5-15.0)
Fasting at blood collection, n (%)[h]	916 (39.3)
Serum creatinine, µmol/l	84.0 (72.0-101.0)
Serum cystatin C, mg/L	0.92 (0.82-1.10)
Highly sensitive C-reactive protein, mg/L	1.66 (0.81-3.62)
eGFR, mL/min per 1.73 m^2	78.5 ± 18.7
Prevalent CKD, n (%)[j]	402 (17.3)

Table 1 continued

	Patients with plasma CE (n=2329)
Systolic BP, mmHg[a]	143.3 ± 21.3
Hypertension, n (%)[q]	2200 (94.6%)
Plasma glucose, mg/L[k]	5.47 (4.97-6.39)
Prevalent diabetes mellitus, n (%)	437 (18.8)
Plasma FA composition, % total FAs	
SFA	13.1 (12.4-13.8)
MUFA	22.4 ± 3.2
PUFA	63.2 (60.5-65.7)
Total n-3 PUFA	2.33 (1.92-2.94)
ALA	0.51 (0.42-0.60)
Total n-6 PUFA	60.5 (57.4-63.2)
AA	8.24 ± 1.98
LA	50.1 (46.9, 53.6)
EPA+DHA	1.72 (1.34, 2.30)
C15:0[l]	0.16 (0.14, 0.19)
C17:0[m]	0.08 (0.00, 0.09)
C14:0	0.72 (0.59, 0.85)
Dietary factors[e]	
Energy, kcal/day	1921.5 ± 521.5
Protein, g/day	70.5 ± 18.8
Saturated fat, g/day	26.8 (20.5-34.3)
LA, g/day	12.3 ± 6.5
ALA, mg/day	936.4 (675.6-1352.9)
EPA+DHA, mg/day	101.4 (40.4-176.4)
Total dairy, g/day[n]	348.7 (220.7, 489.4)
Total fish, g/day[o]	11.8 (4.4, 17.3)
Fiber, g/day	21.2 (16.7-25.6)
Sodium, mg/day[p]	2147.1 (1732.1-2633.8)

Values are reported as mean ± SD for normally distributed variables, median (IQR) for skewed variables, and n (%) for categorical variables. [a] Missing values for 3 (0.1%) patients. [b] Obesity defined as BMI ≥ 30 kg/m^2; underweight defined as BMI < 20 kg/m^2. [c] Missing values for 11 (0.5%) patients. [d] Categorised as "no: 0 g/day", " low: >0-10 g/day" , "moderate: >10-20 g/day for women and >10-30 g/day for men", and " high: >20 g/day for women and >30 g/day for men". [e] Missing values for 166 (7.1%) patients. [f] Anatomical Therapeutic Chemical Classification (ATC) System coding: antithrombotic drugs (B01), anti-hypertensive drugs (C02, C03, C07, C08 and C09), and statins (C10AA and C10B). [g] 12 (0.5%) missing values for total cholesterol and HDL-cholesterol and triglycerides; 114 (4.9%) missing values for LDL-cholesterol. [h] Fasting status defined as having had last meal at least 8h before blood collection. [i] Missing values for 96 (4.1%) patients.[j] CKD defined as eGFR < 60 mL/min per 1.73 m^2. [k] Missing values for 16 (0.7%) patients. [l] C15:0 includes 66 patients with zero value (either non-detectable, or true zero). [m] C17:0 includes 747 patients with zero value (either non-detectable, or true zero). [n] Defined as total milk + total yoghurt + total cheese + dairy desserts + cream + milk for coffee and creamers + butter + ice cream. [o] Defined as ready-bought fried fish + shellfish + trout, gurnard + herring + eel, mackerel, salmon + other kind of fish. [p] Sodium is only estimated from foods and does not include discretionary sources. [q] Hypertension defined as high blood pressure (systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg) or use of antihypertensive drugs. MI, myocardial infarction; BMI, body mass index; LDL-cholesterol, low-density lipoprotein cholesterol; HDL-cholesterol, high-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; BP, blood pressure; FA, fatty acid; SFA, saturated fatty acids; MUFA, mono-unsaturated fatty acids; PUFA, poly-unsaturated fatty acids; ALA, alpha-linolenic acid; AA, arachidonic acid; LA, linoleic acid; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid.

Plasma LA and kidney function decline

Median (IQR) plasma LA was 50 (47-54)% of total FAs in CE (**Table 1**). The mean ± SD annual eGFR decline in the lowest quartile (Q1) of plasma LA was 1.66 ± 3.80 mL/min per 1.73 m^2 as compared to a lower annual eGFR decline in the higher quartiles (Q2-Q4 combined) of plasma LA (1.28 ± 3.78 mL/min per 1.73 m^2, **Table 2**). After multivariable adjustment, the mean (95% CI) annual kidney function decline was +0.40 (0.01;0.78) mL/min per 1.73 m^2 less for patients with higher plasma LA levels (Q2-Q4) as compared to those with lower plasma LA levels (Q1) (**Fig. 1, Table 2**). In continuous analyses, each SD (~5%) increase in plasma LA was not significantly associated with less annual kidney function decline (+0.16 (-0.04;0.35) mL/min per 1.73 m^2). Some evidence was found that the association between plasma LA and annual kidney function decline was modified by diabetes (P interaction = 0.13) or CKD (P interaction = 0.15) with the association being more pronounced in patients with prevalent diabetes (+1.21 (0.24;2.19) mL/min per 1.73 m^2) or prevalent CKD (+0.90 (-0.09;1.89) mL/min per 1.73 m^2). In subsamples of patients with low (below median, ≤1.72%) and high (above median, >1.72%) plasma EPA+DHA, no association was observed (**Fig. 1, Table 2**, P interaction = 0.97)

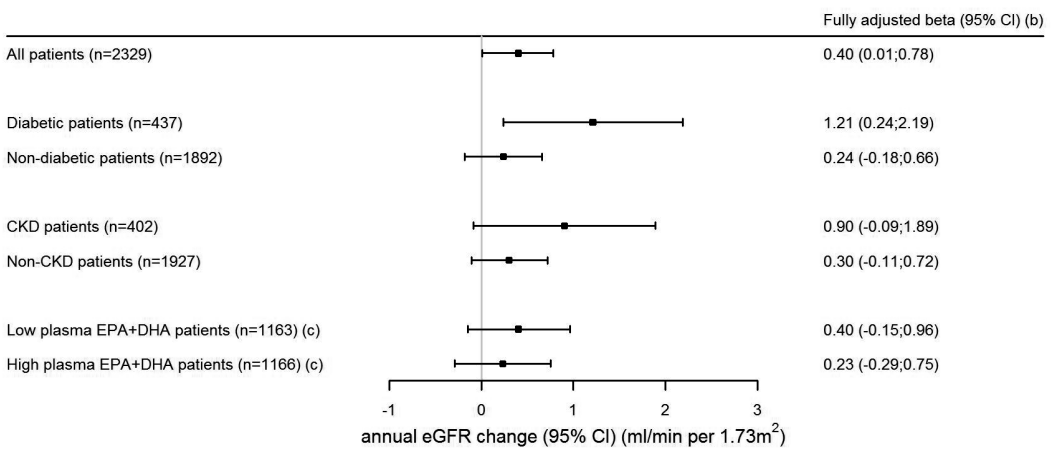

Fig. 1 Forest plot high (Q2-Q4) vs low (Q1) plasma LA in CE and annual eGFR change. (a). Low and high are defined as follows: $Low_{all\ patients}$: ≤46.9%, $high_{all\ patients}$: >46.9%; $low_{diabetic\ patients}$: ≤46.1%, $high_{diabetic\ patients}$: >46.1%; $low_{non\text{-}diabetic\ patients}$: ≤ 46.6%, $high_{non\text{-}diabetic\ patients}$: >46.6%; $low_{CKD\ patients}$: ≤47.4%, $high_{CKD\ patients}$: >47.4%; $low_{non\text{-}CKD\ patients}$: ≤46.8%, $high_{non\text{-}CKD\ patients}$: >46.8%; $low_{low\ plasma\ EPA+DHA\ patients}$: ≤48.6%, $high_{low\ plasma\ EPA+DHA\ patients}$: >48.6%; $low_{high\ plasma\ EPA+DHA\ patients}$: ≤45.7%, $high_{high\ plasma\ EPA+DHA\ patients}$: >45.7%. (b). Adjusted for: age, sex (2 categories), total serum cholesterol, BMI, smoking status (3 categories), alcohol intake (g/day, 4 categories), hypertension (2 categories), hours of fasting before blood collection, statin use (2 categories), plasma C14:0, C15:0, C17:0, and plasma EPA+DHA. (c). Low and high plasma EPA+DHA defined using the median of the distribution (1.72% total FAs in CE). Analyses in strata of low and high plasma EPA+DHA were not adjusted for plasma EPA+DHA. LA, linoleic acid; CE, cholesteryl esters; eGFR, estimated glomerular filtration rate, CI, confidence interval; CKD, chronic kidney disease; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid.

Table 2 Betas and 95% CI for high vs low plasma LA[a] in CE and per SD[b] and annual eGFR change in 2329 post-MI patients from the Alpha Omega Cohort.

	Sample size	Plasma LA		P value	Per SD	P value
All patients, cut-off (% total FAs)	N=2329	Q1 (≤46.9)	Q2-Q4 (>46.9)			
Median (IQR, % total FAs)		44.4 (42.5;45.8)	51.9 (49.4;54.7)			
Mean ± SD annual eGFR change (mL/min per 1.73 m^2)		-1.66 ± 3.80	-1.28 ± 3.78			
Model 1[c]		Ref	0.42 (0.06;0.77)	0.02	0.14 (-0.02;0.30)	0.08
Model 2[d]		Ref	0.40 (0.01;0.78)	0.05	0.16 (-0.04;0.35)	0.11
Diabetic patients[e], cut-off (% total FAs)	N=437	Q1 (≤46.1)	Q2-Q4 (>46.1)			
Median (IQR, % total FAs)		43.8 (41.9;44.8)	51.4 (49.1;54.3)			
Mean ± SD annual eGFR change (mL/min per 1.73 m^2)		-2.44 ± 4.56	-1.89 ± 3.84			
Model 1[c]		Ref	0.90 (0.00;1.79)	0.05	0.16 (-0.23;0.55)	0.42
Model 2[d]		Ref	1.21 (0.24;2.19)	0.02	0.38 (-0.13;0.88)	0.15
Non-diabetic patients, cut-off (% total FAs)	N=1892	Q1 (≤46.6)	Q2-Q4 (>46.6)			
Median (IQR,% total FAs)		44.5 (42.7;46.0)	51.9 (49.5;54.7)			
Mean ± SD annual eGFR change (mL/min per 1.73 m^2)		-1.46 ± 3.55	-1.15 ± 3.76			
Model 1[c]		Ref	0.35 (-0.04;0.74)	0.08	0.12 (-0.04;0.29)	0.15
Model 2[d]		Ref	0.24 (-0.18;0.66)	0.27	0.08 (-0.13;0.29)	0.43
CKD patients[f], cut-off (% total FAs)	N=402	Q1 (≤47.4)	Q2-Q4 (>47.4)			
Median (IQR, % total FAs)		44.3 (42.4;45.9)	52.6 (49.5;55.5)			
Mean ± SD annual eGFR change (mL/min per 1.73 m^2)		-0.66 ± 3.59	0.14 ± 3.93			
Model 1[c]		Ref	0.91 (0.04;1.78)	0.04	0.37 (0.00;0.75)	0.05
Model 2[d]		Ref	0.90 (-0.09;1.89)	0.07	0.43 (-0.09;0.95)	0.10
Non-CKD patients, cut-off (% total FAs)	N=1927	Q1 (≤46.8)	Q2-Q4 (>46.8)			
Median (IQR,% total FAs)		44.4 (42.5;45.8)	51.8 (49.4;54.5)			
Mean ± SD annual eGFR change (mL/min per 1.73 m^2)		-1.84 ± 3.81	-1.60 ± 3.67			
Model 1[c]		Ref	0.29 (-0.09;0.67)	0.14	0.08 (-0.09;0.24)	0.37
Model 2[d]		Ref	0.30 (-0.11;0.72)	0.15	0.11 (-0.09;0.32)	0.29

Table 2 continued

	Sample size	Plasma LA		P value	Per SD	P value
Low plasma EPA+DHA patients[g], cut-off (% total FAs)	N=1163	Q1 (≤48.6)	Q2-Q4 (>48.6)			
Median (IQR, % total FAs)		46.0 (44.1;47.4)	53.3 (51.1;55.7)			
Mean ± SD annual eGFR change (mL/min per 1.73 m^2)		-1.48 ± 4.00	-1.25 ± 3.86			
Model 1[c]		Ref	0.32 (-0.20;0.85)	0.22	0.10 (-0.13;0.33)	0.40
Model 2[d,h]		Ref	0.40 (-0.15;0.96)	0.15	0.17 (-0.10;0.44)	0.21
High plasma EPA+DHA patients[g], cut-off (% total FAs)	N=1166	Q1 (≤45.7)	Q2-Q4 (>45.7)			
Median (IQR,% total FAs)		43.2 (41.6;44.5)	50.1 (47.8;52.8)			
Mean ± SD annual eGFR change (mL/min per 1.73 m^2)		-1.75 ± 3.70	-1.33 ± 3.68			
Model 1[c]		Ref	0.28 (-0.21;0.78)	0.26	0.14 (-0.08;0.35)	0.21
Model 2[d,h]		Ref	0.23 (-0.29;0.75)	0.39	0.16 (-0.09;0.42)	0.21

[a] Plasma LA was analysed in quartiles and subsequently divided in low (Q1) and high (Q2-Q4). [b] The SD of plasma LA was ~5% for all groups. [c] Model 1 was adjusted for age, sex (2 categories), total serum cholesterol level. [d] Model 2 was additionally adjusted for BMI, smoking status (3 categories), alcohol intake (g/day, 4 categories), hypertension (2 categories), hours of fasting before blood collection, statin use (2 categories), plasma C14, C15:0, C17:0, and plasma EPA+DHA. [e] Prevalent diabetes defined as a self-reported physician's diagnosis, use of glucose lowering drugs, or elevated plasma glucose level (≥7.0 mmol/L if fasted for ≥4 h or ≥11.1 mmol/L if not fasted). [f] Prevalent CKD defined as baseline eGFR < 60 mL/min per 1.73 m^2. [g] Low and high plasma EPA+DHA defined using the median (=1.72% total FAs in CE) of the distribution. [h] Analyses in strata of low and high plasma EPA+DHA were not adjusted for plasma EPA+DHA. CI, confidence interval; Q, quartile; LA, linoleic acid; eGFR, estimated glomerular filtration rate; MI, myocardial infarction; FAs, fatty acids; IQR, interquartile range; CKD, chronic kidney disease, EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid.

Plasma EPA+DHA and kidney function decline

Median (IQR) level of combined plasma EPA+DHA was 1.7 (1.3-2.3)% of total FAs in CE of which 1.05% was EPA and 0.66% DHA (Table 1). The mean ± SD annual eGFR decline in the patient group with lower plasma EPA+DHA levels (below median, ≤1.72%) was 1.28 ± 3.88 mL/min per 1.73 m^2. For those with higher plasma EPA+DHA levels (above median, >1.72%), the mean ± SD annual eGFR decline was 1.47 ± 3.69 mL/min per 1.73 m^2 (**Supplemental Table 1**). Higher vs lower plasma EPA+DHA was not associated with eGFR change after multivariable adjustment (-0.12 (-0.45;0.20) mL/min per 1.73 m^2; **Fig. 2, Supplemental Table 1**), which was also confirmed by the continuous analyses (**Supplemental Table 1**). Analyses in strata of diabetes, in those without CKD, or with lower and higher plasma LA levels, yielded similar results (**Fig. 2, Supplemental Table 1**). An indication of effect modification by CKD (P interaction = 0.09) was shown with a stronger, but non-significant association between plasma EPA+DHA and annual kidney function loss in patients with prevalent CKD (**Supplemental Table 1**). However, no indication of effect modification by diabetes (P interaction = 0.46) and plasma LA (P interaction = 0.86) was found.

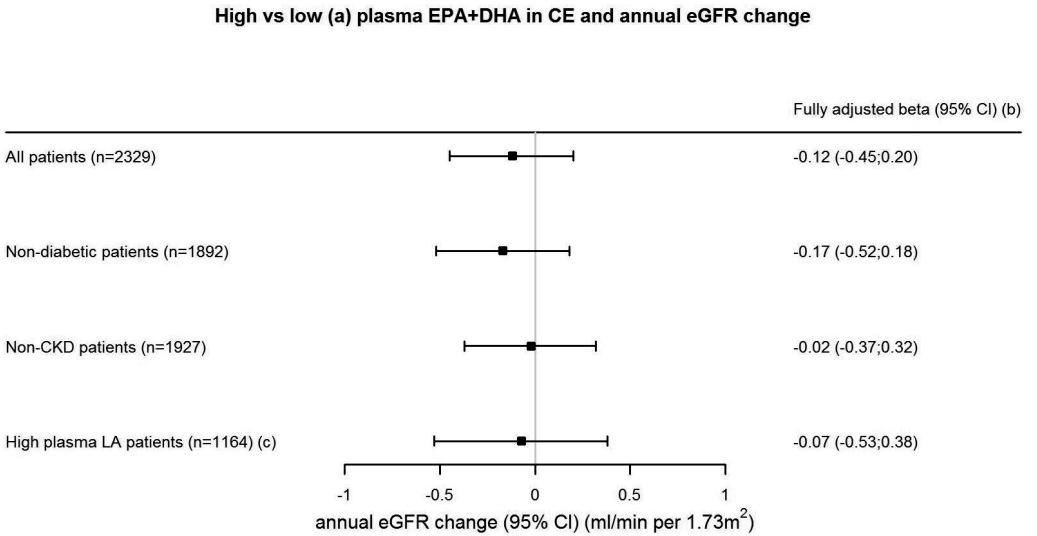

Fig. 2 Forest plot high (above median) vs low (below median) plasma EPA+DHA in CE and annual eGFR change. (a). Low and high are defined as follows: $Low_{all\ patients}$: ≤1.72%, $high_{all\ patients}$: >1.72%; $Low_{non\text{-}diabetic\ patients}$: ≤1.71%, $high_{non\text{-}diabetic\ patients}$: >1.71%; $Low_{non\text{-}CKD\ patients}$: ≤1.72%, $high_{non\text{-}CKD\ patients}$: >1.72%; $Low_{high\ plasma\ LA\ patients}$: ≤1.48%, $high_{high\ plasma\ LA\ patients}$: >1.48%. (b). Adjusted for: age, sex (2 categories), total serum cholesterol, BMI, smoking status (3 categories), alcohol intake (g/day, 4 categories), hypertension (2 categories), hours of fasting before blood collection, statin use (2 categories), plasma C14:0, C15:0, C17:0, and plasma LA. (c). High plasma LA defined using the median of the distribution (50.1% total FAs in CE). Analysis in stratum of high plasma LA was not adjusted for plasma LA. EPA, eicosapentaenoic acid, DHA, docosahexaenoic acid; CE, cholesteryl esters; eGFR, estimated glomerular filtration rate; CI, confidence interval; CKD, chronic kidney disease; LA, linoleic acid.

Plasma OCFAs and C14:0 and kidney function decline

The median (IQR) of plasma OCFAs (C15:0 and C17:0) were <1% of total FAs in CE (**Table 1**). Values for C15:0 were zero or below the detection limit for 66 patients (2.8% of 2329 patients), and values for C17:0 were zero or below the detection limit for 747 patients (32% of 2329 patients). For both plasma OCFAs, a stronger mean ± SD annual eGFR decline in the patient group with higher plasma OCFAs was observed (**Supplemental Table 2, Supplemental Table 3**). After multivariable adjustment, higher (above median, >0.16%) vs lower (below median, ≤0.16%) plasma C15:0 was not associated with eGFR change (-0.27 (-0.63;0.09) mL/min per 1.73 m^2, **Fig. 3, Supplemental Table 2**). This was confirmed by analyses on a continuous scale (**Supplemental Table 2)**. Results were not altered after exclusion of patients with prevalent diabetes or prevalent CKD (**Fig. 3, Supplemental Table 2**). No association was found for patients with prevalent diabetes or prevalent CKD (**Supplemental Table 2**). For plasma C17:0, similar results for all patients and for those without prevalent diabetes or prevalent CKD were observed (**Fig. 3, Supplemental Table 3**). In patients with prevalent diabetes or prevalent CKD, no association was shown between plasma C17:0 and eGFR change (**Supplemental Table 3**). Effect modification by diabetes (P $interaction_{C15:0}$ = 0.53; P $interaction_{C17:0}$ = 0.88) or CKD (P $interaction_{C15:0}$ = 0.46; P $interaction_{C17:0}$ = 0.23) was not observed for both OCFAs.

The median (IQR) of plasma C14:0 was 0.72 (0.59-0.85)% of total FAs in CE (**Table 1**). The mean ± SD annual eGFR decline in both groups of lower (below median, ≤0.72%) and higher (above median, >0.72%) plasma C14:0 were almost equal (**Supplemental Table 4**). After multivariable adjustment, higher vs lower plasma C14:0 was not associated with eGFR change (+0.09 (-0.26;0.44) mL/min per 1.73 m^2, **Fig. 3, Supplemental Table 4**), which was confirmed in analyses on a continuous scale (**Supplemental Table 4**). Results were similar in strata of diabetes and in a subgroup of non-CKD patients (**Fig. 3, Supplemental Table 4**). No association was found for patients with prevalent CKD (**Supplemental Table 4**). Effect modification by diabetes (P interaction = 0.57) or CKD (P interaction = 0.31) was not present in this association.

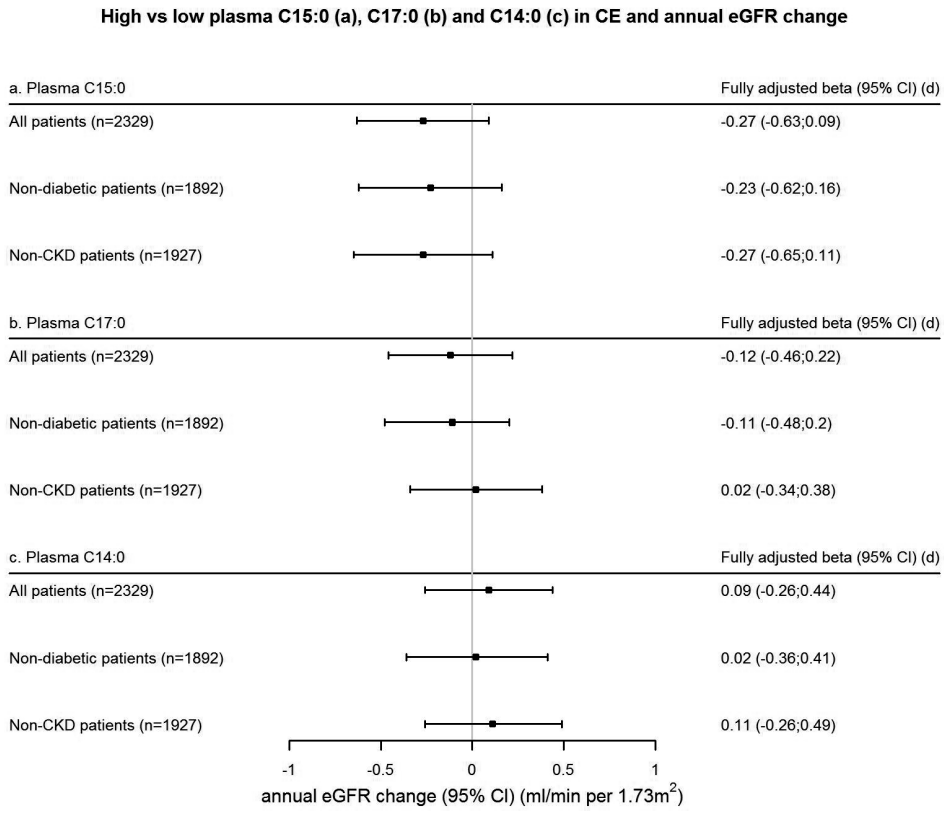

Fig. 3 Forest plot high (above median) vs low (below median) plasma C15:0, C17:0 and C14:0 in CE and annual eGFR change. (a). Low and high are defined as follows: $Low_{all,\ non\text{-}diabetic,\ non\text{-}CKD\ patients}$: ≤0.16%, $high_{all,\ non\text{-}diabetic,\ non\text{-}CKD\ patients}$: >0.16%; all patients group includes 2.8% with non-detectable or true zero; non-diabetic patients group includes 2.5% with non-detectable or true zero; non-CKD patients group includes 3.0% with non-detectable or true zero. (b). $Low_{all,\ non\text{-}diabetic,\ non\text{-}CKD\ patients}$ ≤0.08%, $high_{all,\ non\text{-}diabetic,\ non\text{-}CKD\ patients}$: >0.08%; all patients group includes 32.1% with non-detectable or true zero; non-diabetic patients group includes 32.8% with non-detectable or true zero; non-CKD patients group includes 32.3% with non-detectable or true zero. (c). $Low_{all,\ non\text{-}diabetic\ and\ non\text{-}CKD\ patients}$: ≤0.72%, $high_{all,\ non\text{-}diabetic\ and\ non\text{-}CKD\ patients}$: >0.72% total FAs. (d). Adjusted for: age, sex (2 categories), total serum cholesterol, BMI, smoking status (3 categories), alcohol intake (g/day, 4 categories), hypertension (2 categories), hours of fasting before blood collection, statin use (2 categories), plasma C14:0/C15:0/C17:0, plasma LA, and EPA+DHA. CE, cholesteryl esters; eGFR, estimated glomerular filtration rate; CI, confidence interval; CKD, chronic kidney disease.

Discussion

This study showed that patients with higher plasma LA levels, the most abundant FA in plasma CE, had 40% less kidney function decline after MI. This association was even more pronounced in patients with prevalent diabetes or CKD. Conversely, plasma EPA+DHA, OCFAs, and C14:0, which are present in small amounts in plasma CE, were not associated with kidney function decline.

To the best of our knowledge, this is the first study of multiple plasma FAs in CE and kidney function decline in a large population of stable, drug-treated, post-MI patients. Although GFR was estimated using the combined serum cr and serum CysC CKD-EPI equation and therefore not directly measured, the CKD-EPI eGFR equation is considered a valid tool for use in epidemiological studies (38). Previous analyses in the Alpha Omega Cohort have shown strong associations between eGFR and major CVD risk factors (9) and cause-specific mortality (10). Unfortunately, we had no information about other markers of kidney damage such as proteinuria. Furthermore, patients who died during follow-up (n=233, **Supplemental Figure 1**) were not eligible for studying eGFR change, which required a second blood sample after ~40 months of follow-up. Consequently, we cannot exclude the possibility of a differential association between plasma FAs and kidney function in that small group of patients who were most likely less healthy.

Data on plasma LA and kidney function are scarce, particularly in large patient cohorts. The InCHIANTI study, conducted in 676 generally healthy Italian elderly, has been the only study thus far to observe less kidney function decline over three years of follow-up with higher plasma LA levels (25). Yet, inverse associations between plasma LA measured in various lipid compartments and other CMD, such as CVD and obesity, have been observed in generally healthy populations in several analyses of pooled studies (45, 46). This also included an inverse association of plasma LA in CE with incident diabetes in a previous analysis of post-MI patients from the Alpha Omega Cohort (47). In this present study, the results showed stronger associations between plasma LA levels and kidney function decline in patients with diabetes or CKD compared to the overall analysis. Therefore, this study may suggest an important role of plasma LA in predicting kidney function decline, particularly in metabolically-deranged patients, including diabetes and CKD. Favourable associations of plasma LA with CMD may be attributable to cholesterol-lowering effects, improved glucose metabolism, or reduced inflammation (48). Notably, Pertiwi and colleagues (47) suggested that an impaired liver function due to altered metabolic conditions in patient populations may affect diabetes risk in those with low plasma LA levels. Since the correlation between dietary and plasma LA was only weak in our cohort of post-MI patients (r=0.15), we do not consider high LA intake a likely explanation (29).

Plasma EPA+DHA, an accepted biomarker of fish intake (26), was not associated with kidney function decline in our cohort of post-MI patients. This is in contrast with a previous analysis in the present cohort that showed 30% less kidney function decline after ~40 months of EPA+DHA supplementation (400 mg/day) compared with a placebo (39). In that same analysis, however, supplementation with EPA+DHA and α-linolenic acid (ALA) combined did not significantly affect kidney function (39). Regardless, we cannot exclude the possibility of a chance finding. Beneficial and significant inverse associations for total n-3 PUFAs, which included ALA, EPA and DHA, were also found in the previously described Italian cohort study

(25). However, the population for analysis of the Italian study was considerably smaller (n=676) than the present analysis (n=2329), and chance could therefore explain its findings. Furthermore, Italians have a Mediterranean-type of diet which includes larger amounts of fish, and a previous analysis in the Alpha Omega Cohort showed that dietary EPA+DHA were well reflected in various plasma lipid pools (29). Therefore, a higher fish intake in the InCHIANTI study compared to the low fish intake in Dutch post-MI patients (~12 g/day) may be a possible explanation for discrepant findings.

Previous research indicated that higher dairy intake, particularly low-fat dairy, may be associated with better kidney function (49, 50). This favourable association could be attributed to the high levels of plasma OCFAs present in dairy. Despite a recent study which showed modest correlations between plasma OCFAs and dairy intake in Dutch post-MI patients (51), our analysis of OCFAs with kidney function could not confirm the previous hypothesis that OCFAs may be responsible for the previously observed beneficial associations with kidney function (49, 50). It is believed that dairy minerals, such as higher calcium, potassium, and magnesium, have amongst others, antihypertensive effects, subsequently leading to improved kidney function (50). Plasma C14:0 has also been proposed as a biomarker of dairy intake (52), but it also reflects saturated fat intake from vegetable oils (e.g. coco nut oil and palm oil). However, we found no associations between plasma C14:0 and eGFR change, which is in line with other population-based studies of CMD (22, 24, 27, 28, 53, 54).

Plasma LA may be a good predictor of less kidney function decline, even more so for patients with prevalent diabetes, considering the observed 40% less kidney function decline in the current analysis. It could lead to reduced risks of CKD and premature mortality (10), which would therefore be clinically relevant. Conversely, plasma EPA+DHA, OCFAs, and C14:0 do not seem to be associated with kidney function decline. Ultimately, more long-term studies of plasma LA as a predictor of kidney function decline, a major risk factor for premature mortality, are warranted in cohorts of CHD patients.

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Supplemental Table 1 Betas and 95% CI for high vs low plasma EPA+DHA[a] in CE and per SD[b] and annual eGFR change in 2329 post-MI patients from the Alpha Omega Cohort.

	Sample size	Plasma EPA+DHA		P value	Per SD	P value
All patients, cut-off (% total FAs)	N=2329	Low (≤1.72)	High (>1.72)			
Median (IQR, % total FAs)		1.34 (1.16;1.52)	2.30 (1.98;2.97)			
Mean ± SD annual eGFR change (mL/min per 1.73 m^2)		-1.28 ± 3.88	-1.47 ± 3.69			
Model 1[c]		Ref	-0.20 (-0.50;0.11)	0.21	-0.14 (-0.29;0.01)	0.07
Model 2[d]		Ref	-0.12 (-0.45;0.20)	0.46	-0.10 (-0.26;0.07)	0.25
Diabetic patients[e], cut-off (% total FAs)	N=437	Low (≤1.76)	High (>1.76)			
Median (IQR, % total FAs)		1.37 (1.18;1.56)	2.27 (1.98;2.96)			
Mean ± SD annual eGFR change (mL/min per 1.73 m^2)		-1.94 ± 4.01	-2.14 ± 4.10			
Model 1[c]		Ref	-0.19 (-0.95;0.57)	0.62	0.06 (-0.33;0.44)	0.78
Model 2[d]		Ref	-0.05 (-0.88;0.77)	0.90	0.14 (-0.27;0.55)	0.50
Non-diabetic patients, cut-off (% total FAs)	N=1892	Low (≤1.71)	High (>1.71)			
Median (IQR, % total FAs)		1.34 (1.15;1.51)	2.31 (1.98;2.97)			
Mean ± SD annual eGFR change (mL/min per 1.73 m^2)		-1.12 ± 3.83	-1.33 ± 3.58			
Model 1[c]		Ref	-0.22 (-0.56;0.11)	0.19	-0.18 (-0.35;-0.02)	0.03
Model 2[d]		Ref	-0.17 (-0.52;0.18)	0.35	-0.16 (-0.33;0.02)	0.09
CKD patients[f], cut-off (% total FAs)	N=402	Low (≤1.71)	High(>1.71)			
Median (IQR, % total FAs)		1.30 (1.09;1.50)	2.28 (1.96;3.00)			
Mean ± SD annual eGFR change (mL/min per 1.73 m^2)		0.37 ± 4.04	-0.44 ± 3.66			
Model 1[c]		Ref	-0.80 (-1.54;-0.05)	0.04	-0.29 (-0.66;0.09)	0.13
Model 2[d]		Ref	-0.79 (-1.62;0.04)	0.06	-0.20 (-0.62;0.22)	0.35
Non-CKD patients, cut-off (% total FAs)	N=1927	Low (≤1.72)	High (>1.72)			
Median (IQR, % total FAs)		1.36 (1.17;1.52)	2.30 (1.98;2.96)			
Mean ± SD annual eGFR change (mL/min per 1.73 m^2)		-1.63 ± 3.76	-1.69 ± 3.66			
Model 1[c]		Ref	-0.07 (-0.40;0.26)	0.67	-0.09 (-0.26;0.07)	0.28
Model 2[d]		Ref	-0.02 (-0.37;0.32)	0.90	-0.07 (-0.24;0.11)	0.47

Supplemental Table 1 continued

	Sample size	Plasma EPA+DHA		P value	Per SD	P value
Low plasma LA patients[g], cut-off (% total FAs)	N=1165	Low (≤1.96)	High (>1.96)			
Median (IQR, % total FAs)		1.56 (1.37;1.75)	2.60 (2.21;3.33)			
Mean ± SD annual eGFR change (mL/min per 1.73 m^2)		-1.49 ± 3.70	-1.54 ± 3.72			
Model 1[c]		Ref	-0.07 (-0.50;0.35)	0.74	-0.12 (-0.33;0.09)	0.27
Model 2[d,h]		Ref	0.00 (-0.43;0.43)	0.99	-0.07 (-0.28;0.15)	0.53
High plasma LA patients[g], cut-off (% total FAs)	N=1164	Low (≤1.48)	High (>1.48)			
Median (IQR, % total FAs)		1.20 (1.04;1.33)	2.01 (1.69;2.54)			
Mean ± SD annual eGFR change (mL/min per 1.73 m^2)		-1.24 ± 3.83	-1.24 ± 3.89			
Model 1[c]		Ref	0.00 (-0.44;0.44)	1.00	-0.10 (-0.32;0.12)	0.39
Model 2[d,h]		Ref	-0.07 (-0.53;0.38)	0.75	-0.13 (-0.35;0.10)	0.27

[a] Low and high plasma EPA+DHA defined using the median of the distribution. [b] The SD of plasma EPA+DHA was ~1% for all groups. [c] Model 1 was adjusted for age, sex (2 categories), total serum cholesterol. [d] Model 2 was additionally adjusted for BMI, smoking status (3 categories), alcohol intake (g/day, 4 categories), hypertension (2 categories), hours of fasting before blood collection, statin use (2 categories), plasma C14:0, C15:0, C17:0, and plasma LA. [e] Prevalent diabetes defined as a self-reported physician's diagnosis, use of glucose lowering drugs, or elevated plasma glucose level (≥7.0 mmol/L if fasted for ≥4 h or ≥11.1 mmol/L if not fasted). [f] Prevalent CKD defined as baseline eGFR < 60 mL/min per 1.73 m^2. [g] Low and high plasma LA defined using the median (=50.1% total FAs in CE) of the distribution. [h] Analyses in strata of low and high plasma LA were not adjusted for plasma LA. CI, confidence interval; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; CE, cholesteryl esters; SD, standard deviation; eGFR, estimated glomerular filtration rate; MI, myocardial infarction; FAs, fatty acids; IQR, interquartile range; CKD, chronic kidney disease; LA, linoleic acid.

Supplemental Table 2 Betas and 95% CI for high vs low plasma C15:0[a] in CE and per SD[b] and annual eGFR change in 2329 post-MI patients from the Alpha Omega Cohort.

	Sample size	Plasma C15:0		P value	Per SD	P value
All patients[g], cut-off (% total FAs)	N=2329	Low (≤0.16)	High (>0.16)			
Median (IQR, % total FAs)		0.14 (0.12;0.15)	0.19 (0.17;0.21)			
Mean ± SD annual eGFR change (mL/min per 1.73 m^2)		-1.27 ± 3.95	-1.51 ± 3.57			
Model 1[c]		Ref	-0.16 (-0.48;0.15)	0.30	-0.04 (-0.19;0.12)	0.65
Model 2[d]		Ref	-0.27 (-0.63;0.09)	0.14	-0.06 (-0.25;0.13)	0.53
Diabetic patients[e,g], cut-off (% total FAs)	N=437	Low (≤0.15)	High (>0.15)			
Median (IQR, % total FAs)		0.13 (0.12;0.14	0.18 (0.17;0.21			
Mean ± SD annual eGFR change (mL/min per 1.73 m^2)		-1.81 ± 4.25	-2.26 ± 3.83			
Model 1[c]		Ref	-0.45 (-1.22;0.32)	0.26	-0.02 (-0.41;0.36)	0.90
Model 2[d]		Ref	-0.65 (-1.53;0.24)	0.15	-0.08 (-0.56;0.39)	0.74
Non-diabetic patients[g], cut-off (% total FAs)	N=1892	Low (≤0.16)	High (>0.16)			
Median (IQR,% total FAs)		0.14 (0.12;0.15)	0.19 (0.17;0.21)			
Mean ± SD annual eGFR change (mL/min per 1.73 m^2)		-1.12 ± 3.85	-1.35 ± 3.53			
Model 1[c]		Ref	-0.15 (-0.49;0.19)	0.37	-0.06 (-0.22;0.11)	0.52
Model 2[d]		Ref	-0.23 (-0.62;0.16)	0.24	-0.08 (-0.28;0.13)	0.47

Supplemental Table 2 continued

	Sample size	Plasma C15:0		P value	Per SD	P value
CKD patients[f,g], cut-off (% total FAs)	N=402	Low (≤0.16)	High (>0.16)			
Median (IQR, % total FAs)		0.14 (0.12;0.15)	0.19 (0.18;0.21)			
Mean ± SD annual eGFR change (mL/min per 1.73 m^2)		0.18 ± 4.09	-0.28 ± 3.59			
Model 1[c]		Ref	-0.21 (-0.98;0.56)	0.59	-0.09 (-0.47;0.30)	0.66
Model 2[d]		Ref	0.08 (-0.80;0.97)	0.85	0.04 (-0.44;0.53)	0.86
Non-CKD patients[g], cut-off (% total FAs)	N=1927	Low (≤0.16)	High (>0.16)			
Median (IQR,% total FAs)		0.14 (0.12;0.15)	0.19 (0.17;0.21)			
Mean ± SD annual eGFR change (mL/min per 1.73 m^2)		-1.57 ± 3.86	-1.77 ± 3.52			
Model 1[c]		Ref	-0.09 (-0.42;0.25)	0.61	0.00 (-0.16;0.17)	0.98
Model 2[d]		Ref	-0.27 (-0.65;0.11)	0.17	-0.07 (-0.26;0.13)	0.52

[a] Low and high plasma C15:0 defined using the median of the distribution. [b] The SD of plasma C15:0 was ~0.05% for all groups. [c] Model 1 was adjusted for age, sex (2 categories), total serum cholesterol. [d] Model 2 was additionally adjusted for BMI, smoking status (3 categories), alcohol intake (g/day, 4 categories), hypertension (2 categories), hours of fasting before blood collection, statin use (2 categories), plasma C14:0, C17:0, plasma LA, and EPA+DHA. [e] Prevalent diabetes defined as a self-reported physician's diagnosis, use of glucose lowering drugs, or elevated plasma glucose level (≥7.0 mmol/L if fasted for ≥4 h or ≥11.1 mmol/L if not fasted). [f] Prevalent CKD defined as baseline eGFR < 60 mL/min per 1.73 m^2. [g] All patients group includes 2.8% with non-detectable or true zero, non-diabetic patients group includes 2.5% with non-detectable or true zero, diabetic patients group includes 4.1% with non-detectable or true zero, non-CKD patients group includes 3.0% with non-detectable or true zero, CKD patients group includes 2.2% with non-detectable or true zero. CI, confidence interval; CE, cholesteryl esters; SD, standard deviation; eGFR, estimated glomerular filtration rate; MI, myocardial infarction; FAs, fatty acids; IQR, interquartile range; CKD, chronic kidney disease.

Supplemental Table 3 Betas and 95% CI for high vs low plasma C17:0[a] in CE and per SD[b] and annual eGFR change in 2329 post-MI patients from the Alpha Omega Cohort.

	Sample size	Plasma C17:0		P value	Per SD	P value
All patients[g], cut-off (% total FAs)	N=2329	Low (≤0.08)	High (>0.08)			
Median (IQR, % total FAs)		0.00 (0.00;0.07)	0.09 (0.09;0.10)			
Mean ± SD annual eGFR change (mL/min per 1.73m^2)		-1.31 ± 3.88	-1.44 ± 3.69			
Model 1[c]		Ref	-0.15 (-0.46;0.16)	0.33	-0.01 (-0.17;0.15)	0.89
Model 2[d]		Ref	-0.12 (-0.46;0.22)	0.48	0.01 (-0.16;0.18)	0.90
Diabetic patients[e.g], cut-off (% total FAs)	N=437	Low (≤0.08)	High (>0.08)			
Median (IQR, % total FAs)		0.00 (0.00;0.07)	0.10 (0.09;0.11)			
Mean ± SD annual eGFR change (mL/min per 1.73m^2)		-1.93 ± 4.21	-2.16 ± 3.87			
Model 1[c]		Ref	-0.22 (-0.99;0.55)	0.57	0.00 (-0.39;0.39)	1.00
Model 2[d,e]		Ref	-0.21 (-1.05;0.62)	0.62	0.06 (-0.35;0.47)	0.77
Non-diabetic patients[g], cut-off (% total FAs)	N=1892	Low (≤0.08)	High (>0.08)			
Median (IQR,% total FAs)		0.00 (0.00;0.07)	0.09 (0.08;0.10)			
Mean ± SD annual eGFR change (mL/min per 1.73m^2)		-1.18 ± 3.80	-1.27 ± 3.62			
Model 1[c]		Ref	-0.12 (-0.45;0.22)	0.50	0.01 (-0.16;0.18)	0.89
Model 2[d,e]		Ref	-0.11 (-0.48;0.2)	0.55	0.03 (-0.15;0.21)	0.75

Supplemental Table 3 continued

	Sample size	Plasma C17:0		P value	Per SD	P value
CKD patients[f,g], cut-off (% total FAs)	N=402	Low (≤0.08)	High (>0.08)			
Median (IQR,% total FAs)		0.00 (0.00;0.07)	0.10 (0.09;0.11)			
Mean ± SD annual eGFR change (mL/min per 1.73m^2)		0.27 ± 4.17	-0.44 ± 3.39			
Model 1[c]		Ref	-0.66 (-1.42;0.09)	0.09	-0.13 (-0.51;0.25)	0.50
Model 2[d]		Ref	-0.54 (-1.38;0.29)	0.20	-0.05 (-0.46;0.36)	0.81
Non-CKD patients[g], cut-off (% total FAs)	N=1927	Low (≤0.08)	High (>0.08)			
Median (IQR,% total FAs)		0.00 (0.00;0.07)	0.09 (0.08;0.10)			
Mean ± SD annual eGFR change (mL/min per 1.73m^2)		-1.66 ± 3.69	-1.65 ± 3.73			
Model 1[c]		Ref	-0.01 (-0.34;0.32)	0.94	0.02 (-0.15;0.19)	0.79
Model 2[d]		Ref	0.02 (-0.34;0.38)	0.90	0.05 (-0.13;0.23)	0.59

[a] Low and high plasma C17:0 defined using the median of the distribution. [b] The SD of plasma C17:0 was ~0.05% for all groups. [c] Model 1 was adjusted for age, sex (2 categories), total serum cholesterol. [d] Model 2 was additionally adjusted for BMI, smoking status (3 categories), alcohol intake (g/day, 4 categories), hypertension (2 categories), hours of fasting before blood collection, statin use (2 categories), plasma C14:0, C15:0, plasma LA, and EPA+DHA. [e] Prevalent diabetes defined as a self-reported physician's diagnosis, use of glucose lowering drugs, or elevated plasma glucose level (≥7.0 mmol/L if fasted for ≥4 h or ≥11.1 mmol/L if not fasted). [f] Prevalent CKD defined as baseline eGFR < 60 mL/min per 1.73 m^2. [g] All patients group includes 32.1% with non-detectable or true zero, non-diabetic patients group includes 32.8% with non-detectable or true zero, diabetic patients group includes 29.1% with non-detectable or true zero, non-CKD patients group includes 32.3% with non-detectable or true zero, CKD patients group includes 31.1% with non-detectable or true zero. CI, confidence interval; CE, cholesteryl esters; SD, standard deviation; eGFR, estimated glomerular filtration rate; MI, myocardial infarction; FAs, fatty acids; IQR, interquartile range; CKD, chronic kidney disease.

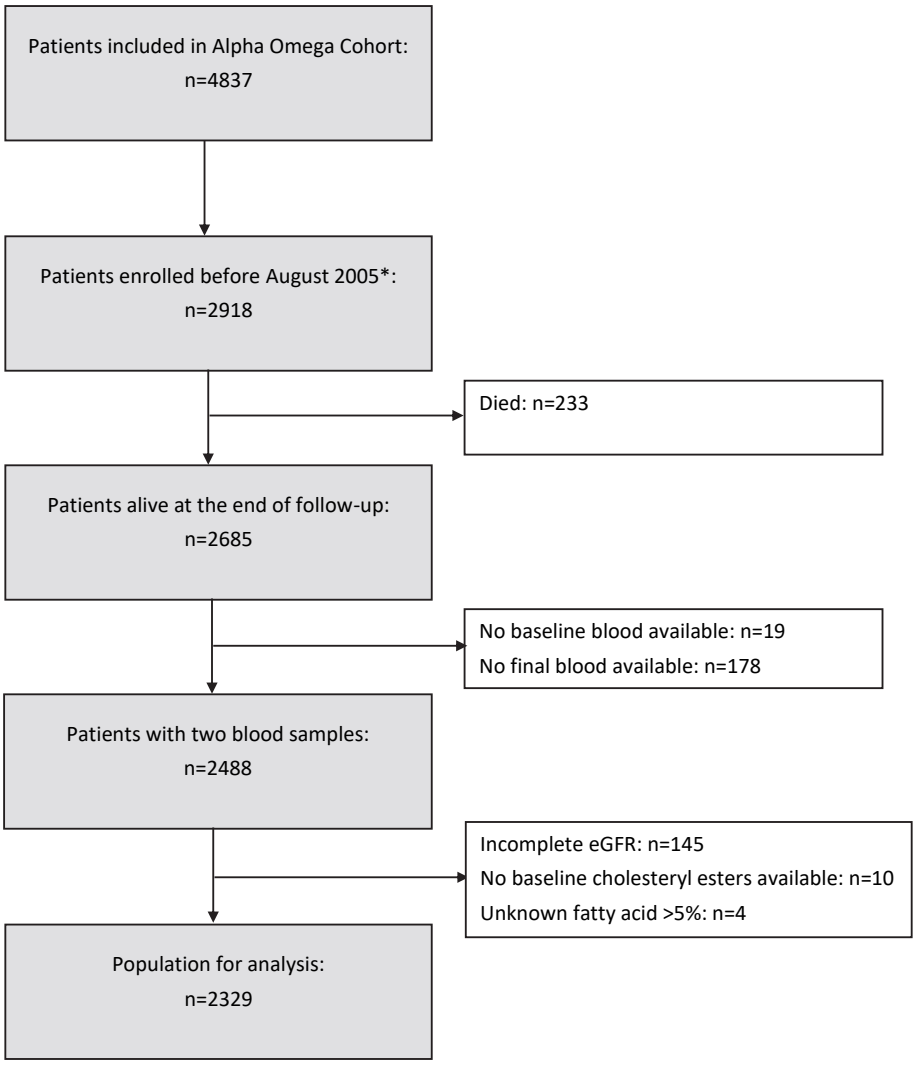
Supplemental Table 4 Betas and 95% CI for high vs low plasma C14:0[a] in CE and per SD[b] and annual eGFR change in 2329 post-MI patients from the Alpha Omega Cohort.

	Sample size	Plasma C14:0		P value	Per SD	P value
All patients, cut-off (% total FAs)	N=2329	Low (≤0.72)	High (>0.72)			
Median (IQR, % total FAs)		0.59 (0.52;0.66)	0.86 (0.78;0.98)			
Mean ± SD annual eGFR change (mL/min per 1.73m^2)		-1.37 ± 3.90	-1.38 ± 3.67			
Model 1[c]		Ref	-0.01 (-0.33;0.30)	0.93	0.02 (-0.14;0.18)	0.80
Model 2[d]		Ref	0.09 (-0.26;0.44)	0.62	0.13 (-0.07;0.32)	0.20
Diabetic patients[e], cut-off (% total FAs)	N=437	Low (≤0.70)	High (>0.70)			
Median (IQR, % total FAs)		0.57 (0.50;0.64)	0.83 (0.77;0.95)			
Mean ± SD annual eGFR change (mL/min per 1.73m^2)		-2.01 ± 4.14	-2.07 ± 3.97			
Model 1[c]		Ref	-0.02 (-0.79;0.76)	0.97	0.11 (-0.28;0.50)	0.58
Model 2[d]		Ref	0.10 (-0.81;1.01)	0.82	0.33 (-0.19;0.85)	0.21
Non-diabetic patients, cut-off (% total FAs)	N=1892	Low (≤0.72)	High (>0.72)			
Median (IQR,% total FAs)		0.59 (0.52;0.66)	0.86 (0.79;0.98)			
Mean ± SD annual eGFR change (mL/min per 1.73m^2)		-1.20 ± 3.79	-1.25 ± 3.62			
Model 1[c]		Ref	-0.07 (-0.41;0.27)	0.68	-0.02 (-0.19;0.15)	0.83
Model 2[d]		Ref	0.02 (-0.36;0.41)	0.90	0.06 (-0.15;0.27)	0.57

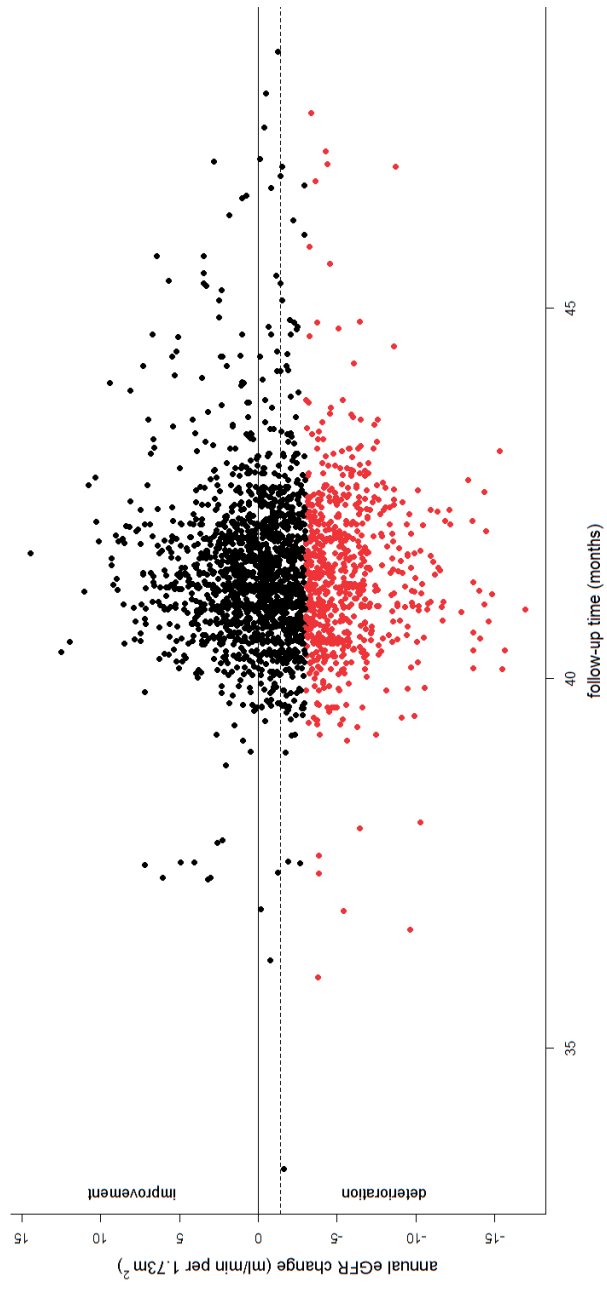
Supplemental Table 4 continued

	Sample size	Plasma C14:0		P value	Per SD	P value
CKD patients[f], cut-off (% total FAs)	N=402	Low (≤0.70)	High (>0.70)			
Median (IQR, % total FAs)		0.58 (0.51;0.64)	0.87 (0.77;0.99)			
Mean ± SD annual eGFR change (mL/min per 1.73m^2)		-0.09 ± 4.23	0.03 ± 3.49			
Model 1[c]		Ref	0.23 (-0.53;0.98)	0.55	-0.13 (-0.51;0.25)	0.49
Model 2[d]		Ref	0.73 (-0.18;1.64)	0.11	0.13 (-0.39;0.66)	0.62
Non-CKD patients, cut-off (% total FAs)	N=1927	Low (≤0.72)	High (>0.72)			
Median (IQR,% total FAs)		0.59 (0.52;0.66)	0.85 (0.78;0.97)			
Mean ± SD annual eGFR change (mL/min per 1.73m^2)		-1.67 ± 3.79	-1.65 ± 3.62			
Model 1[c]		Ref	0.05 (-0.28;0.39)	0.76	0.09 (-0.08;0.25)	0.31
Model 2[d]		Ref	0.11 (-0.26;0.49)	0.55	0.17 (-0.04;0.37)	0.11

[a] Low and high plasma C14:0 defined using the median of the distribution. [b] The SD of plasma C14:0 was ~0.2% for all groups. [c] Model 1 was adjusted for age, sex (2 categories), total serum cholesterol. [d] Model 2 was additionally adjusted for BMI, smoking status (3 categories), alcohol intake (g/day, 4 categories), hypertension (2 categories), hours of fasting before blood collection, statin use (2 categories), plasma C15:0, C17:0, plasma LA, and EPA+DHA. [e] Prevalent diabetes defined as a self-reported physician's diagnosis, use of glucose lowering drugs, or elevated plasma glucose level (≥7.0 mmol/L if fasted for ≥4 h or ≥11.1 mmol/L if not fasted). [f] Prevalent CKD defined as baseline eGFR < 60 mL/min per 1.73 m^2. CI, confidence interval; CE, cholesteryl esters; SD, standard deviation; eGFR, estimated glomerular filtration rate; MI, myocardial infarction; FAs, fatty acids; IQR, interquartile range; CKD, chronic kidney disease.



Supplemental Fig. 1 Flowchart for population for analysis. *Due to financial constraints, only these patients were eligible for follow-up measurements. eGFR, estimated glomerular filtration rate.



Supplemental Fig. 2. Distribution of eGFR change during follow-up in 2329 post-MI patients from the Alpha Omega Cohort. The red coloured dots are patients with rapid kidney function decline (defined as eGFR decline of at least 3 mL/min per 1.73 m^2 per year). The dashed horizontal line represents the mean annual eGFR change. Three patients with follow-up >49 months were omitted from the figure.

Chapter 8

Association of serum uric acid with fatty liver index, kidney function, and 12-year mortality risk in cardiovascular patients

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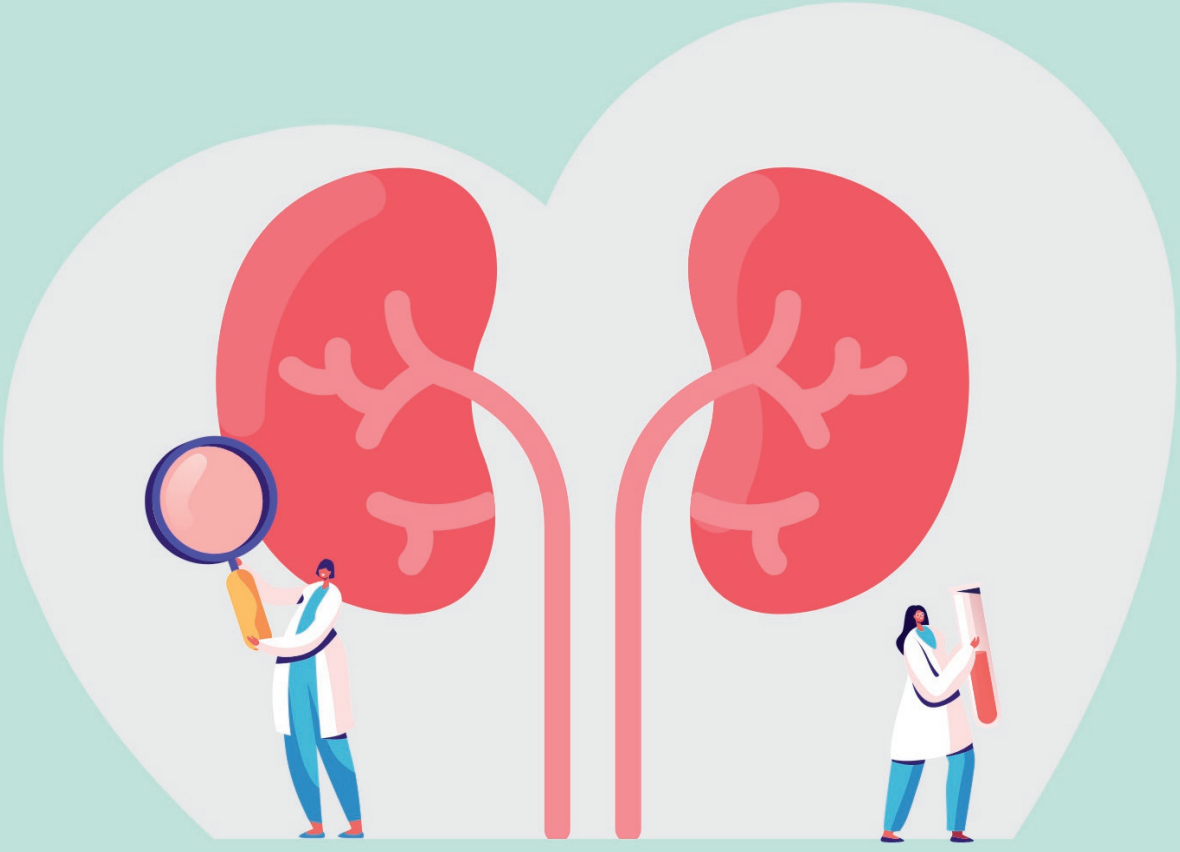
In revision



Abstract

Aims To study associations of non-alcoholic fatty liver disease (NAFLD), chronic kidney disease (CKD), and serum uric acid (SUA) after myocardial infarction (MI), and the relationship of SUA with 12-year mortality risk.

Methods We included 3396 patients (60-80y, 78% male) of the Alpha Omega Cohort. Multivariable prevalence ratios (PRs) were obtained for the association of NAFLD (Fatty Liver Index [FLI] ≥77 [women];≥79 [men]) with CKD (estimated glomerular filtration rate [eGFR] <60 mL/min per 1.73 m^2). We calculated sensitivity and specificity of SUA to detect the (combined) presence and absence of NAFLD and CKD. Cause-specific mortality was monitored from enrolment (2002-2006) through December 2018. Hazard ratios (HRs) for all-cause and cardiovascular disease (CVD) mortality in SUA categories were obtained from multivariable Cox models.

Results Median baseline FLI was 67 (men: 68; women: 64), and mean ± SD eGFR was 81 ± 20 mL/min per 1.73 m^2 (17% with CKD). Sex-specific FLI was associated with higher CKD prevalence ($PR_{tertile3\ vs\ tertile1}$ 1.94; 95% CI 1.57;2.39). Baseline SUA was 0.36 ± 0.09 mmol/L. With increasing SUA concentrations, specificity for the presence of NAFLD, CKD or both increased, and sensitivity decreased. During 12 [IQR 9-14] years of follow-up, 1592 patients died (713 from CVD). HRs ranged from 1.08 (0.88;1.32) for SUA ≤0.25 mmol/L to 2.13 (1.75;2.60) for SUA >0.50 mmol/L vs SUA >0.30-0.35 mmol/L for all-cause mortality. For CVD mortality, HRs ranged from 1.05 (0.77;1.44) to 2.43 (1.83;3.25).

Conclusion NAFLD and CKD were strongly associated, which was reflected by higher SUA concentrations. SUA was a strong predictor of 12-year mortality risk after MI.

Introduction

Non-alcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease worldwide and its prevalence has been increasing in the past decades (1). NAFLD is a condition with a wide spectrum of severity, ranging from simple steatosis to steatohepatitis, fibrosis, and cirrhosis. The fatty liver index (FLI) is a scoring system and an easy tool to predict NAFLD in large observational studies. Chronic kidney disease (CKD) has also emerged as a public health issue in the past decades and is a major cause of death (2). Cross-sectional associations between FLI and higher odds of CKD have been well documented in population-based studies (3, 4) and in diabetic patients (5). However, little is known about this association in patients with established cardiovascular diseases (CVD).

Both NAFLD and CKD have been associated with elevated serum uric acid (SUA) concentrations (6, 7). Studies in healthy populations have demonstrated the prognostic value of SUA for incidence of NAFLD or CKD (8-11). Since previous studies have shown strong associations between NAFLD and CKD (3-5), SUA might also be a marker for the combined presence of both diseases, reflecting an advanced stage of cardiometabolic disorders. SUA was previously associated with a 1.60-fold higher mortality risk in a study of 10,840 Italian post-myocardial infarction (MI) patients (12). However, little is known about SUA, as potential marker of NAFLD and CKD (combined), in relation to (CVD) mortality after MI.

In Dutch post-MI patients of the Alpha Omega Cohort, we studied the association between NAFLD and CKD. We then evaluated the diagnostic performance of SUA to detect the (combined) presence and absence of NAFLD and CKD. Finally, we examined whether SUA as diagnostic marker of NAFLD and CKD, is associated with long-term mortality risk.

Methods

Study design and study population

We used data of the Alpha Omega Cohort, consisting of 4837 drug-treated Dutch patients (aged 60-80 years, 78% men) with a verified history of MI ≤10 years prior to study enrolment. Venous blood samples and data on lifestyle, diet, health, medication use, and anthropometrics were collected at baseline (13, 14). Patients have been continuously monitored for cause-specific mortality. The study was approved by the medical ethics committee of the Haga Hospital (The Hague, the Netherlands). All patients provided oral and written informed consent for long-term follow-up.

The current analysis excluded patients with missing baseline data on FLI components (n=207), on alcohol consumption (n=427), and on eGFR (n=117). We further excluded patients with

heavy alcohol intake (defined as >30 grams/day for men and >20 grams/day for women, n=628), and allopurinol users (n=62), yielding 3396 patients for all analyses (**Supplemental Fig. 1**).

FLI

Baseline FLI was calculated using BMI (kg/m^2), waist circumference (cm), gamma glutamyl-transferase (GGT, in U/L), and triglycerides (mg/dL). The score is validated in a Caucasian population-based cohort and is calculated as follows (15):

$$FLI = \frac{e0.953 * loge(TG) + 0.139 * BMI + 0.718 * loge(ggt) + 0.053 * WC - 15.745}{1 + e0.953 * loge(TG) + 0.139 * BMI + 0.718 * loge(ggt) + 0.053 * WC - 15.745} \cdot 100$$

TG; triglycerides, WC; waist circumference

FLI was categorised into sex-specific tertiles (T1: <49; T2: ≥49-<77; T3: ≥77 for women; T1: <56; ≥T2: 56-<79; T3: ≥79 for men), and T3 was used as indicator of NAFLD. Weight and height were measured at the patients' home or hospital by trained research nurses, and BMI was calculated. Waist circumference (cm) was measured at the midpoint between the bottom rib and the top of the hipbone using a non-elastic tape.

Venous blood samples (30 mL) were drawn fasted (≥8 h, 35% of the analytical sample) or non-fasted and were sent to the laboratory by next-working-day mail service at ambient temperatures. Blood samples were immediately processed and stored at -80 degrees Celsius upon arrival (16). Serum triglycerides were determined in multiple batches by standard assays (Roche Diagnostics; cat. no. 1488872) on an automated analyser (Hitachi 912; Roche Diagnostics) with an inter- and intra-assay coefficient of variation (CV) <10%. Serum GGT was determined in one batch after completion of the cohort by standard assays (Abbott Diagnostics; cat. no. 7D6522) on an automated analyser (ARCHITECT ci8200; Abbott) with an intra- and inter-assay CV <10%.

eGFR and SUA

A particle-enhanced immunonephelometric assay was used to measure serum cystatin C and the modified kinetic Jaffé method was used to measure serum creatinine as described in detail elsewhere (17). We used the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation from 2021 to estimate GFR, which includes both serum creatinine and serum cystatin C (18). CKD was defined as eGFR <60 mL/min per 1.73 m^2 at baseline. SUA was determined from the same venous blood samples using standard assays (Roche diagnostics; cat. no. 03P3922) on an automated analyser (ARCHITECT ci8200; Abbott). Intra- and inter-assay CV were <10%.

Mortality endpoints

Endpoints for the analysis of SUA with mortality risk were all-cause mortality and CVD mortality. Patients were monitored for their vital status from baseline until 31 December 2018 through linkage with municipal registries. Data collection on cause-specific mortality occurred in three phases. During the first 40-months of follow-up (2002-2009), information was obtained from the national mortality registries (Statistics Netherlands, CBS), treating physicians, and close family members. Primary and contributing causes of death were coded by an independent Endpoint Adjudication Committee and described in detail elsewhere (13, 14). After 40-months of follow-up through 2012, mortality data were obtained from CBS for primary and contributing causes of death. From 2013 onwards, data on only primary cause of death were obtained from CBS. Treating physicians filled out an additional cause-of-death questionnaire (response rate: 67%), which was coded by study physicians who were not involved in the current analysis. The endpoint CVD or CHD was allocated to all patients for whom it was a primary or contributing cause of death, based on any of the data sources. Fatal endpoints were coded according to the International Classification of Diseases, 10th revision (ICD-10) (19). CVD mortality comprised CHD (codes I20-I25), cardiac arrest (I46), heart failure (I50), stroke (I60-I69), and undefined sudden death (R96). CHD mortality comprised I20-I25, I46, and R96.

Other measurements

At baseline, data on sociodemographic factors and lifestyle habits were collected through self-administered questionnaires as described in detail elsewhere (13). Smoking status was categorised into four categories (current; former, ≤10 years; former, >10 years; never). Alcohol consumption was assessed with a 203-item validated food frequency questionnaire (20) and ethanol intake (grams/day) was computed. Alcohol consumption was then categorised as abstainers (0 grams/day), light (>0-10 grams/day for men, >0-5 grams/day for women) and moderate consumption (>10-30 grams/day for men, >5-20 grams/day for women). The 2015 Dutch Healthy Diet index (DHD15-index) score was calculated to reflect adherence to dietary guidelines (scale from no adherence [0] to maximal adherence [150]) (21). Liver enzymes (U/L) alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were determined by standard assays (Abbott Diagnostics; cat. No. 8L9222 and 8L9122) on an automated analyser (ARCHITECT ci8200; Abbott) with an inter- and intra-assay CV <10% from stored blood samples. Blood lipids (mmol/L, total serum cholesterol and high-density lipoprotein cholesterol [HDL-c]) and plasma glucose (mmol/L) were analysed using standard kits (Hitachi 912, Roche Diagnostics, Basel, Switzerland). The Friedewald formula was used to calculate low-density lipoprotein cholesterol (LDL-c) (22). Patients with BMI ≥30 kg/m^2 were classified as having obesity. Diabetes mellitus was considered present in case of a self-reported physician's diagnosis, use of glucose-lowering medication or elevated plasma glucose (≥7.0 mmol/L if fasted >4 h or ≥11.0 mmol/L if not fasted). Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured twice on the left arm with the patient

in a seated position, using an automated device (Omron HEM-711) following a 10-minute rest. The values were then averaged. Self-reported medication use was checked by trained research nurses and coded according to the Anatomical Therapeutic Chemical Classification System (ATC) (23): statins (C10AA), antihypertensive drugs (C02, C03, C07, C08, and C09), glucose-lowering drugs (A10), renin-angiotensin-aldosterone system blockers (C09), and diuretics (C03, including thiazides [C03A] and high-ceiling diuretics [C03C]).

Statistical analysis

We visually checked the distribution of the data by using histograms. Baseline characteristics are presented across sex-specific FLI tertiles. Normally distributed variables are presented as means ± standard deviation (SD). Medians and interquartile range (IQR) are used for skewed data, and n(%) for categorical data.

We used Cox proportional hazard regression models with follow-up time equal to 1 and robust variances (prevalence ratios [PRs] and 95% confidence intervals [CIs]), to analyse the association between FLI in sex-specific tertiles (T1 as reference) and prevalent CKD. PRs in the first model were adjusted for age, sex, and fasting state (<8 hours; ≥8 hours). Model two additionally included smoking status (never, former quit ≤10y ago, former quit >10y ago, current), alcohol consumption (abstainers, light, moderate), statin use (yes, no) and time since last MI. To test the robustness of the results, we repeated analyses subsequently excluding patients with obesity or diabetes. The P_{trend} was obtained by analysing sex-specific FLI tertiles as continuous variable. We also analysed the association of FLI as a continuous variable with prevalent CKD using restricted cubic splines (RCS) in men and women separately. Three knots at the 10^{th}, 50^{th}, and 90^{th} percentile were used according to Akaike's Information Criteria, using the median of T1 (30 for women, 41 for men) as the reference. The Wald chi-square test was used to test for nonlinearity.

We analysed the relationship of FLI and eGFR with SUA (all as continuous variables) with RCS and visualised these in 3D plots. We used model two of the previously mentioned FLI-CKD analysis, and we additionally added diuretics use (yes, no) and total serum cholesterol. Furthermore, multivariable linear regression models were used to examine the associations of sex-specific FLI tertiles (T1 as reference) and of prevalent CKD (no CKD as reference) with SUA. We used model two also including diuretics use (yes, no) and total serum cholesterol, and additionally adjusted analyses of FLI for eGFR and vice versa. Analyses were repeated after excluding patients with obesity or diabetes, and thiazides and high-ceiling diuretics use, as these may affect SUA concentrations (24).

We calculated the proportion of patients with the combined absence of NAFLD and CKD, the presence of NAFLD, the presence of CKD, and the combined presence of NAFLD and CKD per interval of 0.05 mmol/L SUA across the range of the 10^{th} to 90^{th} percentile of SUA (0.25-0.50

mmol/L). Sensitivity and specificity analyses were used to assess the diagnostic utility of SUA to detect the four combinations of (combined) presence and absence of NAFLD and CKD. In prospective analyses, we then used Cox proportional hazard regression models (hazard ratios [HRs] with 95% CIs) to examine the association between SUA and (CVD) mortality risk. SUA was analysed in intervals of 0.05 mmol/L across the range of the 10th to 90th percentile (0.25-0.50 mmol/L), and we used >0.30-0.35 mmol/L as the reference. Proportional hazards assumptions were examined by log-minus-log survival plots, and were met. Survival time was defined as the period between date of baseline assessment and date of death or end of follow-up (for participants who survived), whichever came first. Patients who died due to a competing risk were censored, in addition to those who were lost to follow-up and survived until the end of follow-up. One patient was lost to follow-up and censored after 2.9 years. Models were adjusted for the same variables as in the analyses of FLI, eGFR, and SUA. Analyses were repeated after excluding 748 women, 803 obese patients, 696 patients with diabetes, 805 diuretics users, 1698 patients with DHD15-index score <80 (below median-split), or 544 current smokers. We also analysed the association between SUA as continuous variable and (CVD) mortality, using RCS with three knots (10th, 50th, and 90th percentile) and the median of the group >0.30-0.35 mmol/L as the reference (0.33 mmol/L).

Missing data on fasting state (n=61) and time since last MI (n=7) were imputed using multiple imputation with chained equations (with 10 imputations and 10 iterations) using the MICE package (25). The analyses were performed in each imputed dataset separately, and the estimates were subsequently pooled using Rubin's rules (26).

We used RStudio version 3.6.0 for all analyses, and a two-sided p-value <0.05 was considered statistically significant.

Results

Baseline characteristics

The patient characteristics across sex-specific FLI tertiles at baseline are presented in **Table 1**. Patients were 69 ± 6 years old and predominantly male (78%). Patients in FLI T3 were more often light alcohol consumers, had a lower eGFR, and had higher SUA concentrations than patients in FLI T1. Furthermore, 61% of the patients in FLI T3 was obese, 31% had diabetes, and 97% had hypertension.

Table 1 Baseline characteristics of 3396 post-MI patients of the Alpha Omega Cohort across sex-specific FLI tertiles.

	Sex-specific FLI		
	T1 M: <56 W: <49 (n=1133)	T2 M: ≥56-<79 W: ≥49-<77 (n=1131)	T3 M: ≥79 W: ≥77 (n=1132)
FLI	39.0 [27.8, 47.6]	67.2 [61.2, 72.9]	88.7 [83.4, 94.1]
Fasting FLI[a]	39.9 [28.7, 47.8]	66.1 [60.4, 72.0]	88.5 [83.2, 94.1]
Sociodemographic factors			
Age, years	69.5 ± 5.4	69.6 ± 5.5	68.5 ± 5.6
Men, n (%)	883 (77.9)	882 (78.0)	883 (78.0)
Lifestyle			
Smoking status, n (%)			
Never	243 (21.4)	219 (19.4)	156 (13.8)
Former, > 10 y	209 (18.4)	206 (18.2)	190 (16.8)
Former, ≤ 10 y	485 (42.8)	541 (47.8)	603 (53.3)
Current	196 (17.3)	165 (14.6)	183 (16.2)
Alcohol consumption[b], n (%)			
Abstainers	69 (6.1)	68 (6.0)	74 (6.5)
Light	657 (58.0)	685 (60.6)	712 (62.9)
Moderate	407 (35.9)	378 (33.4)	346 (30.6)
DHD15-index score	82.3 ± 13.8	80.2 ± 13.1	78.8 ± 12.7
Kidney function			
eGFR, mL/min per 1.73 m^2	83.4 ± 19.3	80.6 ± 20.1	78.0 ± 21.6
CKD[c], n (%)	146 (12.9)	180 (15.9)	242 (21.4)
SUA, mmol/L	0.33 ± 0.08	0.37 ± 0.09	0.39 ± 0.10
Liver enzymes			
Serum GGT, U/L	25.0 [19.0, 32.0]	32.0 [24.0, 44.0]	42.0 [30.0, 63.0]
Serum ALT[d], U/L	15.0 [11.0, 19.0]	16.0 [13.0, 21.0]	19.0 [14.0, 25.3]
Serum AST, U/L	27.0 [23.0, 31.0]	27.0 [23.0, 32.0]	28.0 [24.0, 33.0]
AST/ALT ratio[a]	1.95 ± 0.76	1.78 ± 0.58	1.62 ± 0.94
Cardiovascular (risk) factors			
Time since MI[d], years	3.05 [1.40, 5.84]	3.53 [1.70, 6.12]	4.15 [1.93, 6.76]
Fasting at blood collection[a], n (%)	452 (41.5)	418 (38.7)	299 (27.4)
BMI, kg/m^2	24.6 ± 2.12	27.3 ± 2.03	31.2 ± 3.53
Obesity, n (%)	3 (0.3)	112 (9.9)	688 (60.8)
Waist circumference, cm	92.8 ± 7.28	101 ± 5.88	111 ± 8.49
Serum blood lipids, mmol/L			
Total cholesterol	4.51 ± 0.91	4.63 ± 0.88	4.85 ± 1.02
LDL cholesterol[d]	2.53 ± 0.79	2.57 ± 0.76	2.57 ± 0.90
HDL cholesterol	1.38 ± 0.35	1.24 ± 0.29	1.16 ± 0.29
Triglycerides	1.20 [0.98, 1.55]	1.69 [1.30, 2.18]	2.31 [1.69, 3.12]
Fasting triglycerides[a]	1.12 [0.93, 1.39]	1.56 [1.18, 1.96]	1.94 [1.51, 2.66]
Hypercholesterolemia[e], n (%)	1079 (95.2)	1087 (96.1)	1095 (96.7)
Plasma glucose[d], mmol/l	5.63 ± 1.46	6.02 ± 1.90	6.87 ± 2.58
Diabetes, n (%)	139 (12.3)	201 (17.8)	356 (31.4)
SBP[d], mmHg	140 ± 21.7	142 ± 21.3	142 ± 21.1
DBP[d], mmHg	78.9 ± 10.7	80.2 ± 11.0	80.9 ± 11.3
Hypertension[f], n (%)	1052 (92.9)	1078 (95.3)	1099 (97.1)

Table 1 continued

	Sex-specific FLI		
	T1 M: <56 W: <49 (n=1133)	T2 M: ≥56-<79 W: ≥49-<77 (n=1131)	T3 M: ≥79 W: ≥77 (n=1132)
Medication use, n (%)			
Statins	986 (87.0)	978 (86.5)	957 (84.5)
Antihypertensives	978 (86.3)	1017 (89.9)	1049 (92.7)
Diuretics	174 (15.4)	259 (22.9)	372 (32.9)
Thiazides	25 (2.2)	49 (4.3)	57 (5.0)
High-ceiling diuretics	119 (10.5)	170 (15.0)	267 (23.6)
RAAS blockers	581 (51.3)	631 (55.8)	694 (61.3)
Diuretics and RAAS blockers	130 (11.5)	187 (16.5)	286 (25.3)

Values are means ± SDs for normally distributed variables, medians [IQRs] for skewed variables, or n (%) for categorical variables. [a] Means ± SDs for fasting FLI and fasting triglycerides are based on n=1169, including only patients who consumed their last meal ≥8 hours before blood sampling. Part of the cohort had missing values for fasting state (n=137). [b] Abstinence, 0 g/d; light, >0-10 g/d for men, >0-5 g/d for women; moderate, >10 g/d for men, >5 g/d for women. [c] Defined as eGFR <60 mL/min per 1.73 m^2. [d] Part of the cohort had missing values for ALT and AST/ALT ratio (n=41), time since last MI (n=34), LDL cholesterol (n=166), plasma glucose (n=15), and SBP and DBP (n=4). [e] Defined as use of lipid-lowering medication or total serum cholesterol levels ≥5 mmol/L. [f] Defined as use of antihypertensives or either SBP ≥140 mmHg or DBP ≥90 mmHg. MI, myocardial infarction; FLI, Fatty Liver Index; DHD15-index, Dutch Healthy Diet 2015 index; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; SUA, serum uric acid; GGT, gamma glutamyl transferase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; LDL-c, low-density lipoprotein cholesterol; HDL-c, high-density lipoprotein cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure; RAAS, renin-angiotensin aldosterone system.

Association between FLI and CKD

At baseline, median [IQR] FLI was 67 [48-83], and mean ± SD eGFR was 81 ± 20 mL/min per 1.73 m^2 (17% with CKD). In T3 of FLI, 21% had CKD, whereas this was 13% in T1 of FLI. After multivariable adjustment, FLI was associated with higher CKD prevalence, with a PR (95% CI) of 1.94 (1.57, 2.39) for patients in T3 vs T1 (**Table 2**). This association was confirmed in RCS in strata of men and women (**Fig. 1**), and remained strong and statistically significant after excluding patients with obesity or diabetes (**Supplemental Table 1**).

Table 2 Associations of sex-specific FLI tertiles with prevalent CKD in 3396 post-MI patients of the Alpha Omega Cohort.

	Sex-specific FLI			P_{trend}
	T1 M: <56 W: <49	T2 M: ≥56-<79 W: ≥49-<77	T3 M: ≥79 W: ≥77	
Prevalent CKD[a]				
Events/n	146/1133	180/1131	242/1132	
Model 1[b]	REF	1.24 (1.00, 1.54)[d]	1.98 (1.61, 2.44)	<0.001
Model 2[c]	REF	1.24 (0.99, 1.54)	1.94 (1.57, 2.39)	<0.001

[a] Defined as estimated glomerular filtration rate <60 mL/min per 1.73 m^2 at baseline. [b] Adjusted for sex, age, and fasting state (<8 hours, ≥8 hours). [c] Additionally adjusted for smoking status (never, former quit ≤10 y ago, former quit >10 y ago, current), alcohol consumption (abstainers, light, moderate), time since last MI, and statin use (yes, no). [d] Prevalence ratio (95% confidence interval) obtained from Cox proportional hazards models, with follow-up time equal to 1, and robust variances (all such values). FLI, Fatty Liver Index; CKD; chronic kidney disease; MI, myocardial infarction.

Fig. 1 Associations of FLI as continuous variable with prevalent CKD among female (n=748, panel A) and male (n=2648, panel B) post-MI patients of the Alpha Omega Cohort. Solid lines represent PRs and dashed lines represent 95% CIs. The histogram represents the distribution of FLI. Three-knot restricted cubic splines was used, with the median of T1 (FLI of 30 for women and 41 for men) as reference point. PRs were adjusted for age, fasting state (<8 hours, ≥8 hours), smoking status (never, former quit ≤10 y ago, former quit >10 y ago, current), alcohol consumption (abstainers, light, moderate), time since last MI, and statin use (yes, no). Prevalent CKD defined as eGFR <60 mL/min per 1.73 m^2. CKD, chronic kidney disease; PR, prevalence ratio; CI, confidence interval; FLI, Fatty Liver Index, MI, myocardial infarction.

Association between FLI, eGFR, and SUA

At baseline, the mean ± SD SUA concentration was 0.36 ± 0.09 mmol/L. Patients in T3 of FLI had on average 0.041 mmol/L (95% CI 0.035, 0.048) higher SUA concentrations than patients in T1 and patients with CKD had on average 0.073 mmol/L (95% CI 0.065, 0.080) higher SUA concentrations than patients without CKD (**Supplemental Table 2**). Results remained similar after excluding patients with obesity or diabetes (**Supplemental Table 2**). After exclusion of patients using thiazides or high-ceiling diuretics, differences in SUA concentrations were slightly larger, especially for CKD. When FLI, eGFR and SUA were analysed as continuous variables in RCS, we observed that patients with the highest FLI and lowest eGFR had the highest SUA concentration, after multivariable adjustment (**Fig. 2**).

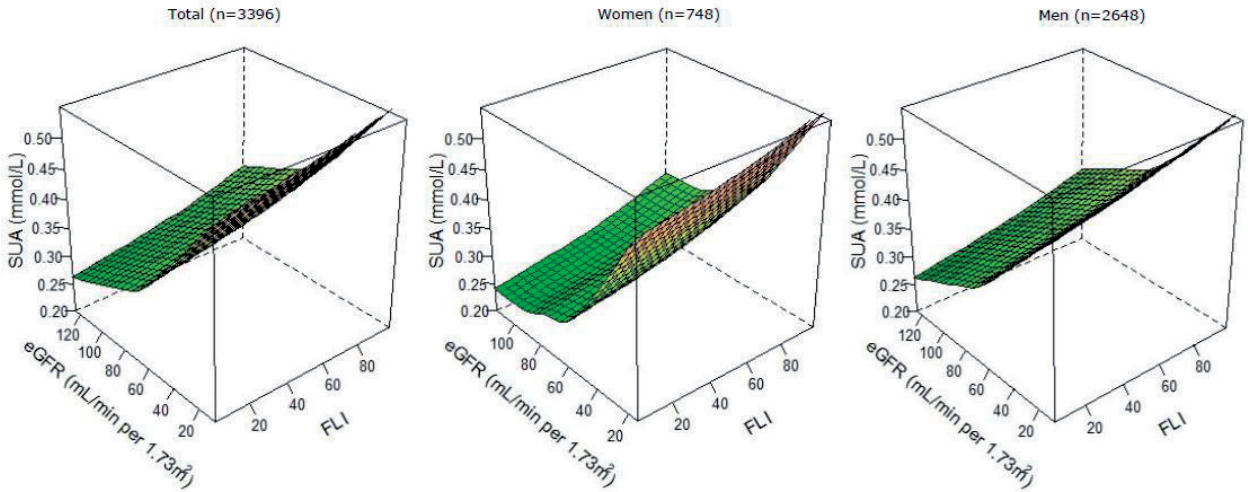
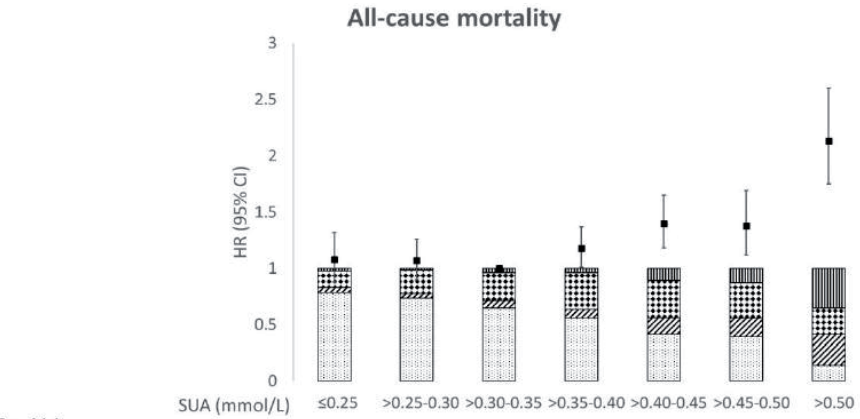


Fig. 2 Associations of FLI and eGFR as continuous variables with SUA, overall, and among female (n=748) and male (n=2648) post-MI patients of the Alpha Omega Cohort. Three-knot restricted cubic splines was used. Values were adjusted for age, sex (except when stratified), fasting state (<8 hours, ≥8 hours), smoking status (never, former quit ≤10 y ago, former quit >10 y ago, current), alcohol consumption (abstainers, light, moderate), time since last MI, statin use (yes, no), total serum cholesterol, and diuretics use (yes, no). FLI, Fatty Liver Index; eGFR, estimated glomerular filtration rate; MI, myocardial infarction; SUA, serum uric acid.

Association of SUA as diagnostic marker of NAFLD and CKD with mortality

In **Fig. 3 and 4**, the proportions of patients with the four combinations of (combined) presence and absence of NAFLD and CKD are presented over the range of SUA concentrations. With higher SUA concentrations, proportions of patients with either NAFLD, CKD or both conditions increased, with the latter group being the largest at SUA concentrations >0.50 mmol/L (35% vs 23% [NAFLD], 28% [CKD], and 14% [none]). With higher SUA concentrations, the specificity for NAFLD, CKD or both increased, and the sensitivity decreased. The highest specificity and lowest sensitivity of SUA to detect NAFLD, CKD or both conditions, was reached at SUA concentrations >0.50 mmol/L.

During a median [IQR] follow-up of 12.4 [8.6-13.8] years, 1592 patients died (713 from CVD). After multivariable adjustment, SUA concentrations ≤0.30 mmol/L were not associated with (CVD) mortality risk (**Fig. 3 and 4, Supplemental Table 3**). However, SUA concentrations >0.35 mmol/L were associated with higher all-cause mortality risk as compared to SUA concentrations >0.30-0.35 mmol/L, with HRs (95% CIs) ranging from 1.18 (1.01, 1.37) for SUA >0.35-0.40 mmol/L through 2.13 (1.75, 2.60) for SUA >0.50 mmol/L. Similarly for CVD mortality, we observed the largest risk estimate for SUA concentrations >0.50 mmol/L (HR 2.43 [95% CI 1.83, 3.25]) (**Fig. 4, Supplemental Table 3**). Associations for (CVD) mortality were supported by RCS in which SUA was analysed as continuous variable (**Supplemental Fig. 2**). Results remained largely similar in sensitivity analyses, such as after exclusion of women, obese, or diabetic patients (**Supplemental Table 4**).



Sensitivity							
Combined absence of NAFLD and CKD	-	0.12	0.34	0.63	0.84	0.93	0.98
Presence of CKD	-	0.97	0.9	0.72	0.57	0.37	0.22
Presence of NAFLD	-	0.96	0.85	0.64	0.37	0.17	0.07
Combined presence of NAFLD and CKD	-	0.98	0.93	0.81	0.71	0.50	0.38
Specificity							
Combined absence of NAFLD and CKD	-	0.95	0.85	0.64	0.43	0.24	0.14
Presence of CKD	-	0.07	0.23	0.48	0.71	0.86	0.93
Presence of NAFLD	-	0.08	0.24	0.49	0.71	0.84	0.92
Combined presence of NAFLD and CKD	-	0.07	0.23	0.48	0.71	0.87	0.94

Fig. 3 Associations between SUA and all-cause mortality risk, proportion of the (combined) absence and presence of NAFLD and CKD, and sensitivity and specificity across categories of SUA among 3396 post-MI patients of the Alpha Omega Cohort. HRs were adjusted for age, sex, fasting state (<8 hours, ≥8 hours), smoking status (never, former quit ≤10 y ago, former quit >10 y ago, current), alcohol consumption (abstainers, light, moderate), time since last MI, statin use (yes, no), total serum cholesterol, and diuretics use (yes, no). NAFLD, non-alcoholic fatty liver disease; CKD, chronic kidney disease; HR, hazard ratio; CI, confidence interval; SUA, serum uric acid; CVD, cardiovascular disease.

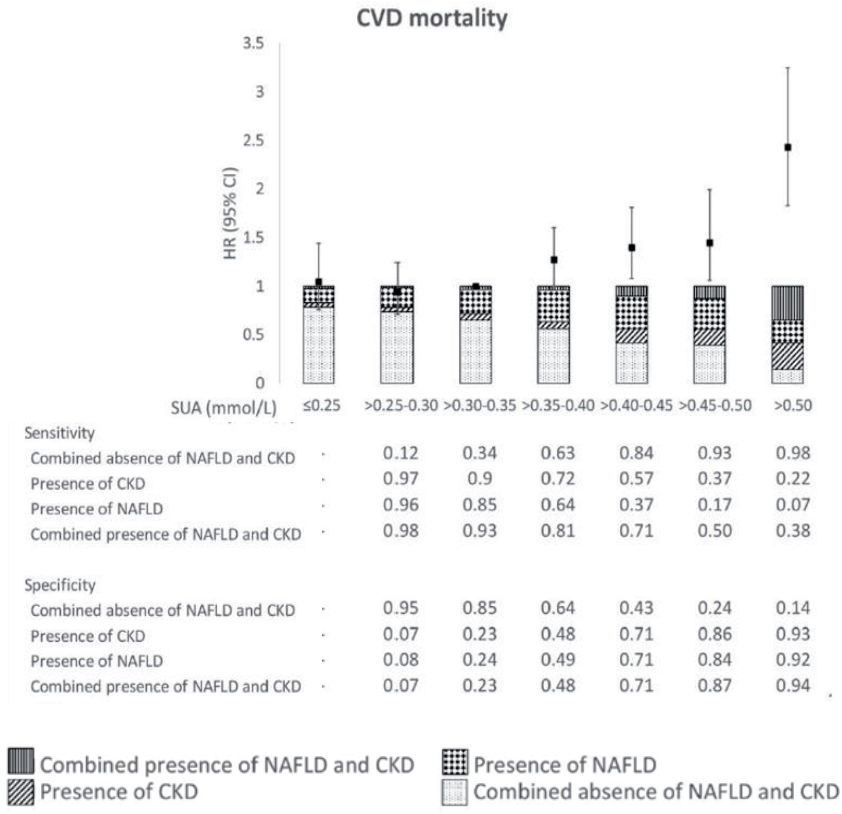


Fig. 4 Associations between SUA and CVD mortality risk, proportion of the (combined) absence and presence of NAFLD and CKD, and sensitivity and specificity across categories of SUA among 3396 post-MI patients of the Alpha Omega Cohort. HRs were adjusted for age, sex, fasting state (<8 hours, ≥8 hours), smoking status (never, former quit ≤10 y ago, former quit >10 y ago, current), alcohol consumption (abstainers, light, moderate), time since last MI, statin use (yes, no), total serum cholesterol, and diuretics use (yes, no). NAFLD, non-alcoholic fatty liver disease; CKD, chronic kidney disease; HR, hazard ratio; CI, confidence interval; SUA, serum uric acid; CVD, cardiovascular disease.

Discussion

Our findings showed a strong cross-sectional association between NAFLD, as assessed by FLI, and CKD in drug-treated post-MI patients. Furthermore, FLI and CKD were positively associated with SUA concentrations at baseline. Finally, SUA as marker of NAFLD and CKD, was associated with a more than 2-fold higher (CVD) mortality risk.

To our knowledge, data on the association between FLI and CKD in post-MI patients is lacking. In a population-based study of 9436 Chinese adults, higher FLI was associated with higher odds of prevalent CKD, in line with our findings (4). A meta-analysis of cross-sectional population-based studies showed that NAFLD, diagnosed by either ultrasound, histology or

biochemistry, was associated with a 2-fold higher odds of prevalent CKD (27). Also in our study among post-MI patients, we found that men and women in the highest vs lowest tertile of FLI had almost 2-fold higher CKD prevalence.

Previous population-based studies have examined the cross-sectional relationship of NAFLD or CKD with SUA, but not of both conditions simultaneously. In 5370 healthy men and women aged 20-74 years of the Third National Health and Nutrition and Examination Survey, participants with hyperuricemia were 40% more likely to have NAFLD (assessed by ultrasound), compared to participants without hyperuricemia (7). Previous Mendelian randomization (MR) studies, using genetic variants to examine causal effects, found no evidence of SUA being a causal risk factor of NAFLD (28, 29). On the contrary, SUA was elevated upon the consequence of NAFLD (28). SUA was positively associated with CKD prevalence in 5808 elderly of the Cardiovascular Health Study (6). A meta-analysis of randomised controlled trials of CKD patients showed that SUA lowering therapy might mitigate the worsening of kidney function (30). However, included trials had a small sample size, there was substantial heterogeneity among trials, and only three out of 12 included studies were double blind and placebo-controlled. Therefore, it remains unclear whether SUA plays a causal role in the development of CKD.

Previous studies in healthy populations found that prevalent CKD (6) and NAFLD (assessed by ultrasonography) (7) were associated with elevated SUA concentrations. With increasing SUA concentrations, we found larger proportions of patients with either NAFLD, CKD, or both conditions, and this was translated into a higher mortality risk. We observed a more than 2-fold higher risk of (CVD) mortality for patients with SUA concentrations >0.50 mmol/L, with patients having both NAFLD and CKD being the largest group. In the GISSI-Prevenzione Trial of 10,840 post-MI patients and 3.5 years follow-up, patients with SUA concentrations >0.38 vs <0.25 mmol/L had a 1.60-fold and 1.40-fold higher risk of all-cause and CVD mortality, respectively (12). More than 85% of patients in the Alpha Omega Cohort was treated according to current therapeutic strategies whereas this was <50% in the GISSI Prevenzione Trial. Untreated cardiovascular risk factors (e.g. blood pressure) in post-MI patients may dilute the association of SUA with mortality, which could explain the differences in mortality risk between the Alpha Omega Cohort and GISSI Prevenzione Trial. Our results showed that SUA could reflect advanced stages of cardiometabolic disorders such as NAFLD and CKD, and is positively associated with mortality risk.

Strengths of the current study include the large cohort of stable post-MI patients with detailed data on potential confounders. Limitations include that we used a proxy measure (FLI) as indicator of NAFLD, whereas imaging techniques are preferred. Yet, FLI is a validated marker (16) based on ultrasonography to predict NAFLD, and is easier to implement in larger groups of patients. Approximately one third of our cohort provided fasting blood samples. Non-

fasting samples may yield higher serum triglyceride and GGT concentrations. However, results did not change after adjustment for fasting state. Third, kidney function was not measured, but estimated. However, eGFR has been widely accepted and used as a valid measure of kidney function in clinical practice (18). Finally, due to the observational design of the current study, we cannot prove that SUA is a causal risk factor of mortality.

To conclude, our results show that NAFLD and CKD are strongly related in post-MI patients. The strong interrelationship between NAFLD and CKD is in turn reflected by elevated SUA concentrations and associated with higher mortality risks. Further research is warranted as to whether the addition of SUA to standard risk markers or NAFLD and CKD combined, improves risk assessment in post-MI patients.

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Conflicts of interest

TV reports grants from Erasmus MC, Erasmus University, Delft University, The European Society for Clinical Nutrition and Metabolism, National Dairy Association, and European Union. JMG reports grants from the Ministry of Health, Welfare and sports in the Netherlands, and the European Union. EB and IK have no conflicts of interest to declare.

Authors' contributions

LH, ACvW, TV, and JMG designed the study; LH and ACvW analysed the data; LH, ACvW, TV, and JMG interpreted the results; LH and ACvW drafted the manuscript; LH, ACvW, IK, EB,TV, and JMG revised the manuscript; all authors approved the final version of the manuscript.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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Supplemental Table 1 Sensitivity analyses for associations of sex-specific FLI tertiles[a] with prevalent CKD in post-MI patients of the Alpha Omega Cohort.

	Sex-specific FLI			
	T1 M: <56 W: <49	T2 M: ≥56-<79 W: ≥49-<77	T3 M: ≥79 W: ≥77	P_{trend}
Prevalent CKD[b]				
No obesity (n=2593)				
Events/n	145/1130	164/1019	93/444	
Model 2[c]	REF	1.28 (1.02, 1.60)[d]	1.87 (1.43, 2.44)	<0.001
No diabetes (n=2700)				
Events/n	125/994	139/930	147/776	
Model 2	REF	1.20 (0.94, 1.53)	1.78 (1.40, 2.27)	<0.001

[a] Sex-specific FLI tertiles are based on n=3396. [b] Defined as estimated glomerular filtration rate <60 mL/min per 1.73 m^2 at baseline. [c] Adjusted for sex, age, fasting state, smoking status, alcohol consumption, time since last MI, and statin use. [d] Prevalent ratios (95% confidence intervals) obtained from Cox proportional hazards models, with follow-up time equal to 1, and robust variances (all such values), using T1 as the reference. FLI, Fatty Liver Index; CKD; chronic kidney disease; MI, myocardial infarction.

Supplemental Table 2 Sensitivity analyses for associations of sex-specific FLI tertiles[a] and prevalence of CKD with SUA in post-MI patients of the Alpha Omega Cohort.

	Sex-specific FLI			CKD[b]	
	T1 M: <56 W: <49	T2 M: ≥56-<79 W: ≥49-<77	T3 M: ≥79 W: ≥77	No	Yes
SUA (mmol/L)					
Total					
N	1133	1132	1132	2828	568
Mean ± SD	0.33 ± 0.08	0.37 ± 0.09	0.39 ± 0.10	0.35 ± 0.08	0.44 ± 0.12
Model 1[c]	REF	0.033 (0.026,0.041)[e]	0.064 (0.057,0.072)	REF	0.098 (0.090,0.106)
Model 2[d]	REF	0.024 (0.018,0.031)	0.041 (0.035,0.048)	REF	0.073 (0.065,0.080)
No obesity (n=2593)					
N	1130	1019	444	2191	402
Mean ± SD	0.33 ± 0.08	0.37 ± 0.09	0.40 ± 0.10	0.34 ± 0.08	0.43 ± 0.12
Model 2	REF	0.024 (0.017,0.030)	0.043 (0.034,0.051)	REF	0.074 (0.065,0.082)
No diabetes (n=2700)					
N	994	930	776	2289	411
Mean ± SD	0.33 ± 0.08	0.37 ± 0.09	0.39 ± 0.09	0.35 ± 0.08	0.43 ± 0.12
Model 2	REF	0.027 (0.021,0.034)	0.044 (0.037,0.051)	REF	0.068 (0.060,0.076)
No thiazide users (n=3265)					
N	1108	1082	1075	2728	537
Mean ± SD	0.33 ± 0.08	0.36 ± 0.09	0.39 ± 0.10	0.35 ± 0.08	0.44 ± 0.12
Model 2	REF	0.027 (0.020,0.033)	0.048 (0.042,0.055)	REF	0.090 (0.083,0.098)
No high-ceiling users (n=2840)					
N	1014	961	865	2489	351
Mean ± SD	0.32 ± 0.07	0.35 ± 0.07	0.38 ± 0.08	0.34 ± 0.07	0.40 ± 0.10
Model 2	REF	0.026 (0.020,0.032)	0.045 (0.038,0.051)	REF	0.060 (0.052,0.068)

[a] Sex-specific FLI tertiles are based on n=3396. [b] Defined as eGFR <60 mL/min per 1.73 m^2 at baseline. [c] Adjusted for sex, age, and fasting state. [d] Additionally adjusted for smoking status, alcohol consumption, time since last MI, statin use, diuretics use (but not when thiazide or high-ceiling diuretics users were excluded), total serum cholesterol, and FLI (for analyses of eGFR with SUA) or eGFR (for analyses of FLI with SUA). [e] β (95% confidence intervals) obtained from multivariable linear models (all such values), using T1 of FLI or no CKD as reference. FLI, Fatty Liver Index; eGFR, estimated glomerular filtration rate; SUA, serum uric acid; CKD, chronic kidney disease; SD, standard deviation; MI, myocardial infarction.

Supplemental Table 3 Associations of baseline SUA with 12-year risk of all-cause and CVD mortality in 3396 post-MI patients of the Alpha Omega Cohort.

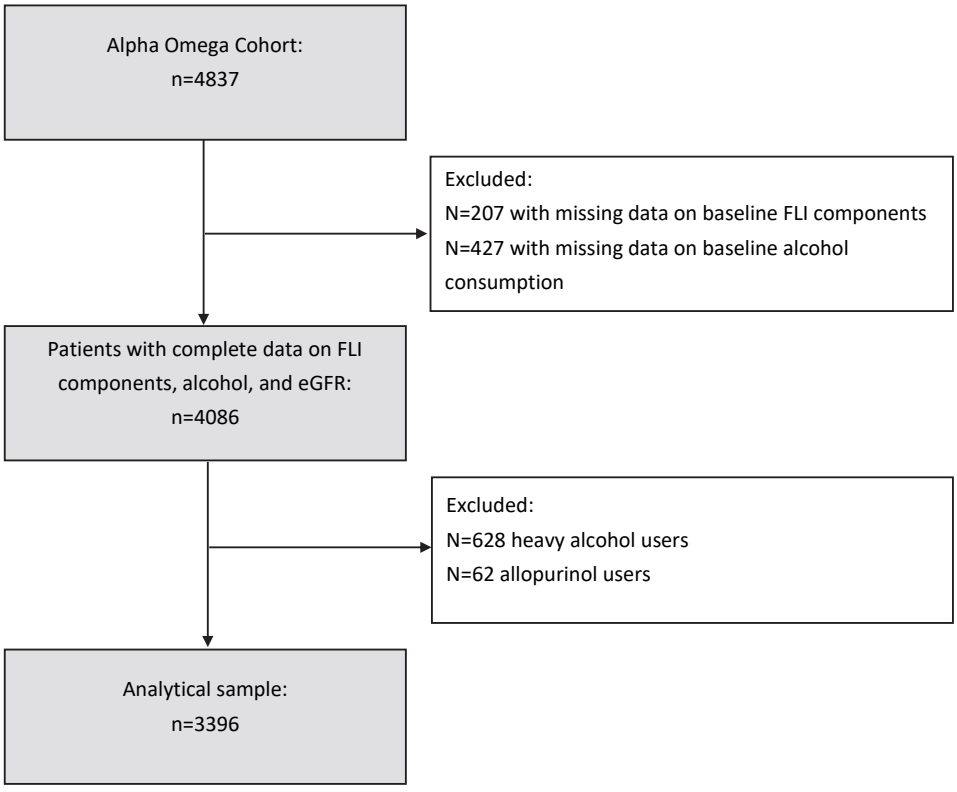
	SUA (mmol/L)							
	≤0.25	>0.25-0.30	>0.30-0.35	>0.35-0.40	>0.40-0.45	>0.45-0.50	>0.50	P_{trend}
All-cause mortality								
Events/n	136/307	236/565	344/871	324/716	247/459	132/235	173/243	
Person-years	3539	6551	10,179	8067	4854	2474	1958	
Model 1[a]	1.08 (0.88, 1.31)[c]	1.06 (0.90, 1.26)	REF	1.19 (1.02, 1.38)	1.46 (1.24, 1.73)	1.59 (1.30, 1.94)	2.75 (2.29, 3.30)	<0.001
Model 2[b]	1.08 (0.88, 1.32)	1.07 (0.90, 1.26)	REF	1.18 (1.01, 1.37)	1.40 (1.18, 1.65)	1.38 (1.12, 1.69)	2.13 (1.75, 2.60)	<0.001
CVD mortality								
Events/n	56/307	91/565	148/871	152/716	108/459	62/235	96/243	
Person-years	3539	6551	10,179	8067	4854	2474	1958	
Model 1	1.01 (0.73, 1.39)	0.95 (0.73, 1.24)	REF	1.29 (1.02, 1.62)	1.50 (1.17, 1.95)	1.81 (1.34, 2.44)	3.54 (2.71, 4.61)	<0.001
Model 2	1.05 (0.76, 1.44)	0.94 (0.72, 1.24)	REF	1.26 (1.00, 1.60)	1.40 (1.08, 1.81)	1.45 (1.06, 1.99)	2.43 (1.83, 3.25)	<0.001

[a] Adjusted for sex, age, and fasting state (<8 hours, ≥8 hours). [b] Additionally adjusted for smoking status (never, former quit ≤10 y ago, former quit >10 y ago, current), alcohol consumption (abstainers, light, moderate), time since last MI, statin use (yes, no), total serum cholesterol, and diuretics use (yes, no). [c] Hazard ratios (95% confidence intervals) obtained from Cox proportional hazards models (all such values), using SUA >0.30-0.35 mmol/L as the reference. SUA, serum uric acid; MI, myocardial infarction; CVD, cardiovascular disease.

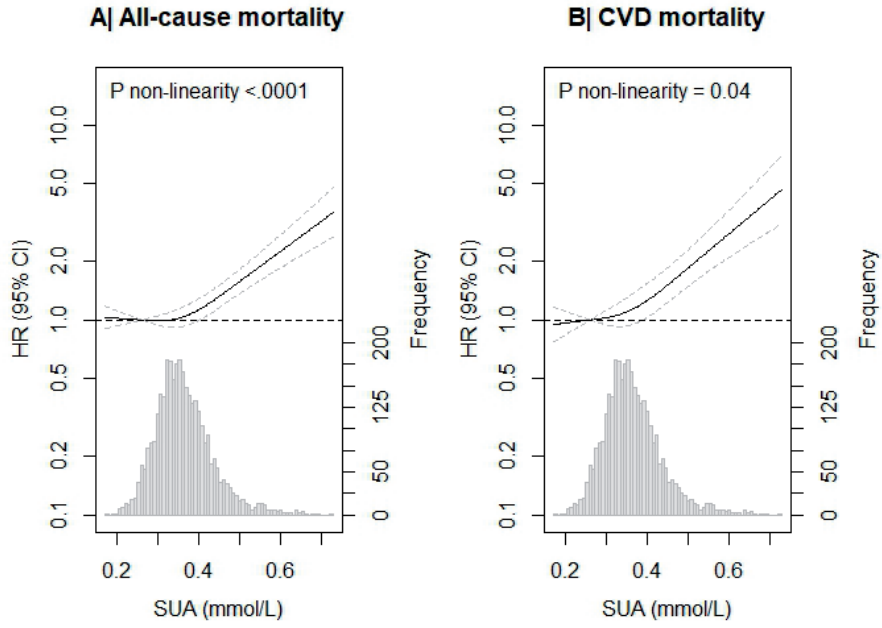
Supplemental Table 4 Sensitivity analyses for baseline categories of SUA and risk of all-cause and CVD mortality in post-MI patients of the Alpha Omega Cohort.

	SUA (mmol/L)						
	≤0.25	>0.25-0.30	>0.30-0.35	>0.35-0.40	>0.40-0.45	>0.45-0.50	>0.50
All-cause mortality							
Men (n=2648)	1.10 (0.85,1.42)[a]	1.18 (0.97,1.42)	REF	1.24 (1.04,1.47)	1.39 (1.15,1.67)	1.42 (1.13,1.79)	2.04 (1.63,2.56)
No obesity (n=2593)	1.13 (0.91,1.40)	1.08 (0.90,1.30)	REF	1.22 (1.02,1.46)	1.46 (1.21,1.77)	1.41 (1.11,1.79)	2.14 (1.69,2.72)
No diabetes (n=2700)	1.05 (0.83,1.33)	1.04 (0.86,1.25)	REF	1.16 (0.98,1.38)	1.43 (1.18,1.72)	1.46 (1.15,1.86)	2.06 (1.63,2.61)
No diuretics (n=2591)	1.03 (0.83,1.29)	1.12 (0.94,1.35)	REF	1.14 (0.96,1.37)	1.37 (1.12,1.67)	1.44 (1.09,1.90)	2.48 (1.75,3.51)
High DHD15-index (n=1698)	0.95 (0.71,1.27)	0.99 (0.78,1.26)	REF	1.10 (0.88,1.37)	1.15 (0.90,1.46)	1.35 (1.00,1.81)	1.95 (1.47,2.58)
No current smokers (n=2852)	1.21 (0.96,1.53)	1.17 (0.97,1.42)	REF	1.13 (0.95,1.34)	1.37 (1.14,1.65)	1.47 (1.17,1.84)	2.11 (1.69,2.62)
CVD mortality							
Men (n=2648)	1.23 (0.82, 1.85)	1.16 (0.86, 1.85)	REF	1.44 (1.10, 1.88)	1.39 (1.00, 1.94)	1.76 (1.23, 2.50)	2.59 (1.84, 3.65)
No obesity (n=2593)	1.17 (0.80, 1.71)	0.97 (0.59, 1.20)	REF	1.36 (1.01, 1.82)	1.37 (0.99, 1.91)	1.58 (1.10, 2.27)	2.49 (1.77, 3.52)
No diabetes (n=2700)	1.12 (0.78, 1.60)	0.97 (0.71, 1.32)	REF	1.34 (1.02, 1.76)	1.44 (1.06, 1.94)	1.70 (1.16, 2.48)	2.51 (1.78, 3.54)
No diuretics (n=2591)	1.01 (0.68, 1.49)	0.97 (0.71, 1.32)	REF	1.29 (0.95, 1.74)	1.30 (0.93, 1.83)	1.85 (1.09, 2.73)	3.16 (1.81, 5.50)
High DHD15-index (n=1698)	1.09 (0.65, 1.83)	0.93 (0.60, 1.46)	REF	1.57 (1.08, 2.28)	1.14 (0.74, 1.77)	1.81 (1.21, 2.83)	3.19 (1.89, 5.37)
No current smokers (n=2852)	1.19 (0.82, 1.75)	0.96 (0.70, 1.17)	REF	1.21 (0.93, 1.56)	1.30 (0.97, 1.73)	1.57 (1.12, 2.20)	2.56 (1.88, 3.50)

[a] HR (95% confidence intervals) obtained from Cox proportional hazards models (all such values), using SUA >0.30-0.35 mmol/L as the reference. HRs are adjusted for sex (but not when stratified), age, fasting state, smoking status (but not when stratified), alcohol consumption, time since last MI, statin use, total serum cholesterol, and diuretics use (but not when stratified). SUA, serum uric acid; MI, myocardial infarction; HR, hazard ratio; CVD, cardiovascular disease; DHD15-index, Dutch Healthy Diet 2015 index.



Supplemental Fig. 1 Flowchart for selection of the analytical sample of the Alpha Omega Cohort. Heavy alcohol consumption is defined as >20 g/day for women and >30 g/day for men. FLI, fatty liver index; eGFR estimated glomerular filtration rate.



Supplemental Fig. 2 Associations of SUA as continuous variable with risk of all-cause (A) and CVD mortality (B) among 3396 post-MI patients of the Alpha Omega Cohort. Solid lines represent HRs and dashed lines represent 95% CIs. The histogram represents the distribution of SUA. Three-knot restricted cubic splines was used, with the median SUA level of the middle SUA category (i.e., >0.30-0.35) as reference point (0.33). HRs were adjusted for age, sex, fasting state, smoking status, alcohol consumption, time since last MI, statin use, total serum cholesterol, and diuretics use. CVD, cardiovascular disease; HR, hazard ratio; CI, confidence interval; SUA, serum uric acid; MI, myocardial infarction.

Chapter 9

General discussion

This thesis aimed to investigate associations of nutritional factors with parameters of kidney function decline in general populations and cardiovascular patients. We additionally examined relations with the fatty liver index (FLI), as predictor of non-alcoholic fatty liver disease (NAFLD), and long-term mortality risk. This thesis is divided into three parts: part A focuses on overall diet and diet quality, part B on coffee and dairy as specific dietary components, and part C on blood biomarkers, including n-6, n-3 and odd-chain fatty acids (OCFAs; i.e., C15:0 and C17:0) and serum uric acid (SUA). Chronic kidney disease (CKD) and cardiovascular disease (CVD) are closely linked: CVD is the leading cause of death in CKD patients, and CVD patients have a higher risk of CKD because of their accelerated kidney function decline. The global CVD prevalence is high, and will likely increase even more the coming years. At the same time, survival of patients who experienced a cardiovascular event has improved, because of improved medical treatment and advanced medication. CKD is a major problem among the growing CVD population. Therefore, it is important to understand the role of nutritional factors in the prevention of kidney function decline and CKD in CVD patients. Research findings on nutritional factors and CKD prevention among general populations cannot be merely translated to a setting with CVD patients: CVD patients have an altered metabolism due to the presence of cardiovascular risk factors and underlying disease process, and their medication use may affect the associations of nutritional factors with kidney function decline.

The results of this thesis were derived from studies in population-based cohorts (**Chapters 2, 4 and 5**) and in stable CVD patients of the Alpha Omega Cohort (**Chapters 3, 6, 7 and 8**). In this final chapter, the main findings of this thesis are summarised and discussed. Furthermore, methodological aspects are considered, and directions for future research and implications for clinical practice, are given.

Table 1 Overview of main findings of this thesis, by risk of kidney function decline.

	Risk of kidney function decline		
	(Trend towards) lower risk	**(Trend towards) higher risk**	**Neutral risk**
Dietary patterns and diet quality	Ch. 2: DASH diet (in healthy participants)	Ch. 2: High-fat, high-sugar diet (in healthy participants)	Ch. 2: Healthy Diet Score (in healthy participants)
	Ch. 2: Mediterranean diet (in healthy participants)	Ch. 2: Dietary acid load (in healthy participants)	Ch. 3: DHD-CVD index (in CVD patients)
	Ch. 2: AHEI (in healthy participants)		
Foods and beverages	Ch. 2: Low-fat dairy (in healthy participants)	Ch. 2 and 3: Red meat (in healthy participants and CVD patients)	Ch. 3: Processed meat (in CVD patients)
	Ch. 2: Allium, non-fermented vegetables (in healthy participants)	Ch. 2: Processed meat (in healthy participants)	Ch. 2: Poultry (in healthy participants)
	Ch. 2 and 3: Nut consumption (in healthy participants and CVD patients)	Ch. 3: Total dairy (in CVD patients)	Ch. 2 and 3: Fish (in healthy participants and CVD patients)
	Ch. 2: Legumes (in healthy participants)	Ch. 6: Total yoghurt, low-fat yoghurt (in CVD patients)	Ch. 2: Full-fat dairy (in healthy participants)
	Ch. 2 and 5: Coffee (in healthy participants)	Ch. 3: Legumes (in CVD patients)	Ch. 6: Total milk, low-fat milk (in CVD patients)
	Ch. 4 and 5: Coffee (in various high risk subgroups, including type 2 diabetes patients)	Ch. 3: Tea (in CVD patients)	Ch. 6: Hard cheeses (in CVD patients)
		Ch. 2: SSBs (in healthy participants)	Ch. 6: Dairy-based desserts (in CVD patients)
		Ch. 3: Alcohol (in CVD patients)	Ch. 2: Fermented, nitrate-containing vegetables (in healthy participants)
			Ch. 3: All sorts of vegetables (in CVD patients)
			Ch. 2 and 3: Fruit (in healthy participants and CVD patients)
			Ch. 4: Coffee (in healthy participants)
			Ch. 2: Tea (in healthy participants)
			Ch. 3: SSBs and fruit juices (in CVD patients)
			Ch. 2: Diet beverages (in healthy participants)
			Ch. 3: Whole grain products (in CVD patients)
			Ch. 3: Sodium (in CVD patients)
			Ch. 3: Plant sterol or stanol-enriched products (in CVD patients)

Table 1 continued

	Risk of kidney function decline		
	(Trend towards) lower risk	**(Trend towards) higher risk**	**Neutral risk**
Blood biomarkers	Ch. 7: Plasma LA in CE (in CVD patients)	Ch. 8: SUA (in CVD patients)	Ch. 7: Plasma EPA + DHA in CE (in CVD patients) Ch. 7: Plasma OCFAs in CE (in CVD patients) Ch. 7: Plasma C14:0 in CE (in CVD patients)

DASH, Dietary Approaches to Stop Hypertension; AHEI, (Alternative) Healthy Eating Index; DHD-CVD index, Dutch Healthy Diet Cardiovascular Disease index; CVD, cardiovascular disease; SSBs, sugar-sweetened beverages; LA, linoleic acid; CE, cholesteryl esters; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; SUA, serum uric acid.

Main findings

In **Table 1**, an overview of the main findings of this thesis by risk of kidney function decline is presented.

Dietary intake and diet quality in general populations and cardiovascular patients

In a literature review of population-based prospective cohort studies, an overall healthier diet was associated with delayed kidney function decline and lower risk of CKD (all risk ratios (RR) <0.90 for highest vs lowest scores on healthy dietary patterns, **Chapter 2)**. For specific foods and beverages, the evidence was more variable and weaker. Higher intakes of low-fat dairy, allium and non-fermented vegetables, legumes, nut consumption and coffee were associated with (a trend towards) lower risk of kidney function decline (**Chapter 2**). A higher risk of kidney function decline was observed for highest vs lowest intakes of red (processed) meat (RR ≥1.12) and sugar-sweetened beverages (SSBs, RR ≥1.37). Neutral associations were observed for intakes of full-fat dairy, fermented and nitrate-containing vegetables, fish, poultry, fruit, tea, and diet beverages (**Chapter 2**). However, such healthy dietary patterns for CKD prevention may not be merely translated to CVD patients, who are treated with lipid-lowering agents and anti-hypertensive drugs **(Chapter 3)**. In **Chapter 3**, adherence to the 2023 Dutch dietary guidelines for CVD patients as summarised in the Dutch Healthy Diet Cardiovascular Disease (DHD-CVD) index, was not associated with kidney function decline in the Alpha Omega Cohort. For individual DHD-CVD food groups, higher adherence scores for guidelines that promote sufficient nut intake, and limit the intake of red meat, were related with less kidney function decline, whereas higher adherence scores for guidelines that promote legumes and dairy were associated with more kidney function decline. Adherence to the other DHD-CVD items (vegetables, fruit, whole grain products, fish, SSBs and fruit juices, tea, processed meat, sodium and plant sterol or stanol-enriched products) were not associated with kidney function decline (**Chapter 3**). Furthermore, effect modification by genetic risk of CKD was not present for overall diet quality. Associations for adherence to guidelines for DHD-CVD

components and kidney function decline among patients with a strong genetic predisposition to CKD, were also generally in line with results of the main analysis (**Chapter 3**).

Coffee and dairy in general populations and cardiovascular patients

Coffee was investigated in Chapter 2, for which I observed a potential beneficial association with kidney function decline in general populations. In **Chapters 4 and 5**, this association was studied in more detail using data of two population-based cohorts. In the Rotterdam Study (RS, **Chapter 4**) and the Lifelines Cohort Study (**Chapter 5**), participants consumed on average around three cups of coffee per day, which is similar to intake in the average Dutch population in the food consumption survey 2012-2016 (1). In the RS (~5.4 years follow-up), coffee consumption was not associated with kidney function decline in the total population, but an indication for improved kidney function was observed among older aged (≥70 y), with type 2 diabetes, with obesity, and former smokers (**Chapter 4**). In the large population-based Lifelines Cohort Study (~3.6 years follow-up), each extra cup of coffee was associated with 0.03 mL/min per 1.73 m^2 less kidney function decline and 3% lower risk of CKD, also in various higher risk populations (**Chapter 5**). All associations persisted after exclusion of non-coffee drinkers. Dairy was investigated in Chapters 2 and 3, and contrasting associations were observed. Low-fat dairy intake was beneficially associated with kidney function decline (Chapter 2), but total dairy (irrespective of fat content) as part of the DHD-CVD index was adversely associated (Chapter 3). Specific dairy products (milk, hard cheeses, yoghurt, and dairy desserts) may have differential effects on cardiometabolic health, and I investigated this further in **Chapter 6**. The median energy-adjusted intakes of the four main dairy products ranged between 18 grams/day (total yoghurt) and 70 grams/day (dairy desserts). Here, intake of milk, hard cheeses, and dairy desserts were not associated with kidney function. For yoghurt, however, I observed more kidney function decline with a flattened curve at higher intakes (**Chapter 6**).

Blood biomarkers in cardiovascular patients

Plasma fatty acids (FAs; LA, EPA and DHA, OCFAs, and C14:0) in cholesteryl esters (CE) were studied in relation to kidney function decline among stable CVD patients in **Chapter 7**. The median plasma LA level was 50% of total FAs, and this was <2% for plasma EPA+DHA, OCFAs and C14:0. Higher levels of plasma EPA+DHA (derived from fatty fish), OCFAs (derived from dairy) and C14:0 (derived from dairy, coconut or palm oil) were not associated with kidney function decline. However, higher levels of plasma LA were associated with 40% less kidney function decline, particularly among patients with diabetes or CKD (**Chapter 7**). Apart from nutritional biomarkers, I also studied the link between SUA (as alternative biomarker of kidney function), FLI, CKD, and long-term mortality risk. In a cross-sectional analysis, the FLI as predictor of NAFLD was associated with CKD, and SUA was in turn associated with higher FLI and lower estimated glomerular filtration rate (eGFR). In a prospective analysis, I observed

that SUA was associated with >2-fold higher risk of (CVD) mortality (**Chapter 8**). Those with the highest CVD mortality risk had the highest prevalence of NAFLD and CKD combined.

Interpretation of the findings

Kidney function decline and CKD prevalence in different cohorts

In the Alpha Omega Cohort, the CKD prevalence (defined as eGFR <60 mL/min per 1.73 m^2) was between 10 and 20% in all of my studies, depending on which version of the Chronic Kidney Disease Epidemiology (CKD-EPI) Collaboration equation was used. This proportion was comparable with the proportion of CKD in elderly individuals at high CVD risk of the PREDIMED Study (2). However, CKD was more prevalent among patients of the Valsartan in Acute Myocardial Infarction Trial (VALIANT) (3). The average annual eGFR decline was approximately 1.4 mL/min per 1.73 m^2 in the cohort of post-MI patients. Other patient cohorts reported a wide range of annual eGFR decline, with an average annual decline of 0.8 mL/min per 1.73 m^2 per year in patients of the MONICA registry (4), and 2.2 mL/min per 1.73 m^2 per year among PREVEND study participants who experienced an ischemic event (5). In the CATS randomised trial, kidney function declined on average with 0.5 mL/min per 1.73 m^2 per year in ACE inhibitor users, whereas this was 5.4 mL/min per 1.73 m^2 per year in placebo users (6). In the Alpha Omega Cohort, 43% of the patients used ACE inhibitors at baseline (7), which may explain the lower annual eGFR decline in this cohort vs other MI patient cohorts.

Although the definitions of CKD differed slightly between the RS and the Lifelines Cohort Study, both studies found a similar proportion of participants who developed CKD during the study period (13% in RS and 11% in Lifelines Cohort Study). In a previous systematic review of 26 population-based studies, the CKD prevalence was ~7% in adults aged 30 years and older, and ranged between 23% and 36% in individuals of 64 years and older (8). In the RS and Lifelines Cohort Study, CKD prevalence was considerably lower, which is likely due to differences in use of eGFR equations (Modification of Diet in Renal Disease (MDRD) study equation in the systematic review (8) and CKD-EPI equation in the RS and the Lifelines Cohort Study). The MDRD study equation is developed in patients with established CKD, and overestimates CKD prevalence in general populations (9). The CKD-EPI equation was developed in CKD patient cohorts and population-based studies, and therefore provides a more accurate estimate of GFR in non-CKD populations.

Diet quality

With recommendations to lower the intake of sodium, potassium, phosphorus and protein-rich foods and drinks, dietary strategies to limit CKD progression and prevent kidney failure in advanced-stage CKD patients are well-documented (10). In my literature review of population-based cohort studies with >3 years of follow-up (**Chapter 2**), I observed a lower risk of CKD

when participants scored higher on the Dietary Approaches to Stop Hypertension (DASH) diet, the Mediterranean diet, and the (Alternative) Healthy Eating Index. My findings support previous (systematic) reviews of population-based studies, which have shown improved kidney function parameters if participants better adhered to healthy dietary patterns, such as the DASH diet and the Mediterranean diet (11-15).

However, I observed no association between the DHD-CVD index and kidney function decline in post-MI patients of the Alpha Omega Cohort, also not across strata of genetic CKD risk (**Chapter 3)**. To date, only one previous study on healthy dietary patterns and kidney function decline in CVD patients has been performed (16), and there are no previous studies that also took genetic CKD risk into account. In the CORDIOPREV randomised controlled trial (86% on lipid-lowering agents and 90% on anti-hypertensive drugs) (16), the effect of a Mediterranean diet vs a low-fat diet on kidney function decline was compared after five years of follow-up. The authors observed that the Mediterranean diet resulted in less eGFR decline than the low-fat diet, particularly among those with comorbid type 2 diabetes and those with mildly impaired eGFR (defined as eGFR of 60-90 mL/min per 1.73 m^2). In subgroups of patients with diabetes, obesity, or CKD, neutral results for the DHD-CVD index remained similar. In patients with established CKD of the Chronic Renal Insufficiency Cohort (CRIC), diet was examined in relation to CKD progression. In this study, the top vs bottom tertiles of adherence to the Mediterranean diet and DASH diet were favourably associated with CKD progression (17).

In the PREDIMED trial of elderly participants at high risk of CVD, the effect of a one-year consumption of three different dietary interventions (two Mediterranean-type of diets vs one control low-fat diet) on kidney function was investigated. A pre-post intervention improvement of kidney function was observed as a result of adherence to each of the three diets, but there were no differences in effect on kidney function between the three diets. There was also no additional benefit in terms of kidney function among participants with type 2 diabetes (2). Although the thresholds and cut-offs used in Mediterranean diets in the CORDIOPREV trial and the PREDIMED study differed from the DHD-CVD index, the overall message that a healthier or higher diet quality could delay kidney function decline in CVD patients and individuals at high risk of CVD, is promising. Differences between the two trials (2, 16) and my study may be related to differences in study design (intervention studies vs prospective cohort study). Other explanations for the differences could be length of follow-up (one year and five years in the trials and 3.4 years in the Alpha Omega Cohort), and a higher habitual intake of (fatty) fish and olive oil, which are considered cardioprotective (18-20), in the CORDIOPREV and PREDIMED trials than in the Alpha Omega Cohort. Another explanation could be related to tea or dairy. A guideline for promoting tea intake and dairy (up to a maximum of 450 g/d) was included in the DHD-CVD index, but higher absolute intakes were associated with more kidney function decline in **Chapter 3**. **Table 2** provides an overview of components, cut-offs, and thresholds that were used in various diet quality

scores in high risk populations (16, 17). Higher cut-offs were used for vegetables and fruit intake in the Mediterranean diet and DASH diet as compared to the DHD-CVD index. Possibly, higher intakes of vegetables and fruit are needed for slowing down kidney function decline. Differences in medication use are unlikely to explain the discrepant results, because this was generally similar across the three studies.

Insights from this thesis Healthy dietary patterns, such as the DASH diet and Mediterranean diet, likely prevent CKD in apparently healthy populations. In CVD patients, however, the DHD-CVD index based on the Dutch dietary guidelines was not associated with kidney function decline. The preferred dietary pattern that should be recommended for CKD prevention after MI warrants further research.

Table 2 Overview of components, cut-offs and thresholds used in various diet quality scores in high risk populations[a].

Component	DHD-CVD[b]		Mediterranean diet[c]		DASH diet[d]		HEI-2015[e]	
	Minimum (0 points)	Maximum (10 points)	Minimum (0 points)	Maximum (1 point)	Minimum (1 points)	Maximum (5 points)	Minimum (0 points)	Maximum (5 points)
Vegetables	0 g/d	≥200 g/d	<400 g/d	≥400 g/d	1.1 servings/d	4.6 servings/d	0 cups/1000 kcal	≥1.1 cups/1000 kcal
Greens and beans							0 cups/1000 kcal	≥0.2 cups/1000 kcal
Fruit[f]	0 g/d	≥200 g/d	<450 g/d	≥450 g/d	0.7 servings/d	4.1 servings/d	0 cups/1000 kcal	≥0.8 cups/1000 kcal
Whole fruit							0 cups/1000 kcal	≥0.4 cups/1000 kcal
Whole grain products[g]	0 g/d of whole grain products OR ratio of whole grains to refined ≤0.7	0 g/d of refined cereal products OR ratio of whole grains to refined grains ≥11			0.1 servings/d	2.4 servings/d	0 g/1000 kcal	≥42 g/1000 kcal
Refined grains							≥127 g/1000 kcal	≤51 g/1000 kcal
Legumes[h]	0 g/d	≥10 g/d	<64 g/d	≥64 g/d	0.3 servings/d	1.5 servings/d		
Nuts[h]	0 g/d	≥15 g/d	<13 g/d	≥13 g/d				
Dairy	0 g/d OR ≥750 g/d	300-450 g/d					0 cups/1000 kcal	≥1.3 cups/1000 kcal
Low-fat dairy[i]					0.1 servings/d	2.3 servings/d		
Fish	0 g/d	≥21 g/d						
Fish and seafood			<43 g/d	43-65 g/d				
Seafood or plant protein							0 g/1000 kcal	≥23 g/1000 kcal
Tea	0 g/d	≥450 g/d						
Fats and oils	0 g/d of soft margarines, liquid cooking fats and vegetable oils OR ratio of liquid cooking fats to solid cooking fats ≤0.6	0 g/d of butter, hard margarines and cooking fats OR ratio of liquid cooking fats to solid cooking fats ≥13						

Table 2 continued

Component	DHD-CVD[b]		Mediterranean diet[c]		DASH diet[d]		HEI-2015[e]	
	Minimum (0 points)	**Maximum (10 points)**	**Minimum (0 points)**	**Maximum (1 point)**	**Minimum (1 points)**	**Maximum (5 points)**	**Minimum (0 points)**	**Maximum (5 points)**
Fat spread[j]			Yes	No				
Olive oil			No	Yes				
			<40 g/d	≥40-60 g/d				
Coffee	Any consumption of unfiltered coffee	Consumption of filtered coffee only OR no coffee consumption						
Red meat[k]	≥100 g/d	≤45 g/d	≥100-150 g/d (red meat) ≥ 60 g/d (processed meat)	<100-150 g/d (red meat) <60 g/d (processed meat)	1.8 servings/d	0.4 servings/d		
Processed meat[k]	≥50 g/d	0 g/d						
Preference for white meat			No	Yes				
SSBs and fruit juices	≥250 g/d	0 g/d						
SSBs[l]			≥1 drink/d	<1 drink/d	1.2 servings/d	0 servings/d		
Commercial bakery products, sweets and pastries			>7 g/d	≤7 g/d				
Total protein							0 g/1000 kcal	≥71 g/1000 kcal
(MUFA+PUFA)/SFA							≤1.2	≥2.5
Saturated fats							≥16% energy	≤8% energy
Alcohol								
Women	≥20 g/d ethanol	≤10 g/d ethanol	<1 glass/d of red wine	1 glass/d of red wine				
Men	≥30 g/d ethanol	≤10 g/d ethanol	<1 glass/d of red wine	2 glasses/d of red wine				
Salt	≥3.8 g/d sodium	≤1.9 g/d sodium			2.676 g sodium	1.041 g sodium	≥2.0 g/1000 kcal	≤1.1 g/1000 kcal

Table 2 continued

Component	DHD-CVD[b]		Mediterranean diet[c]		DASH diet[d]		HEI-2015[e]	
	Minimum (0 points)	Maximum (10 points)	Minimum (0 points)	Maximum (1 point)	Minimum (1 points)	Maximum (5 points)	Minimum (0 points)	Maximum (5 points)
Plant sterol or stanol-enriched products	0 g/d	>0 g/d						
Added sugars							≥26% energy	≤6.5% energy
Sofrito[m]			<2 times/w	≥2 times/w				

[a] High risk populations are CVD patients of the Alpha Omega Cohort, CHD patients of the CORDIOPREV trial (16), and CKD patients of the CRIC study (17). [b] DHD-CVD index was not associated with kidney function decline in this thesis. [c] As assessed in the CORDIOPREV trial. The Mediterranean diet produced less eGFR decline than the low-fat diet (16). [d] As assessed in the CRIC study. Adherence to the DASH diet was associated with lower risk of CKD progression in patients with established CKD (17). Cut-offs and thresholds that were used were not clear from this study. Therefore, I used cut-offs and thresholds from the Nurses' Health Study (21). [e] As assessed in the CRIC study. Adherence to the HEI-2015 was associated with lower risk of CKD progression in patients with established CKD. Cut-offs and thresholds used are from Hu et al. 2021 (17). [f] Fruit in the Mediterranean diet and DASH diet also includes natural fruit juices (16, 21). [g] Whole grain foods in the DASH diet are brown rice, dark breads, cooked cereals, whole grain cereals, other grains, popcorn, wheat germ, and bran (21). [h] Nuts and legumes are included as one component in the DASH diet, and included foods are nuts, peanut butter, dried beans, peas, and tofu (21). [i] Low-fat dairy foods in the DASH diet are skim milk, yoghurt, and cottage cheese (21). [j] Fat spread foods in the Mediterranean diet are butter and margarine (16). [k] Red and processed meat are included as one component in the DASH diet and Mediterranean diet, and included foods are beef, pork, lamb, deli meats, organ meats, hot dogs, and bacon (16, 21). [l] SSBs in the DASH diet and Mediterranean diet are carbonated and noncarbonated sweetened beverages (16, 21). [m] Sofrito is a sauce made with tomato and onion, often including garlic and aromatic herbs, and slowly simmered with olive oil (16). DHD-CVD, Dutch Healthy Diet Cardiovascular Disease; DASH diet, Dietary Approaches to Stop Hypertension diet; HEI-2015, Healthy Eating Index 2015; SSBs, sugar-sweetened beverages; MUFA, mono-unsaturated fatty acids; PUFA, poly-unsaturated fatty acids; SFA, saturated fatty acids; CVD, cardiovascular disease; CHD, coronary heart disease; CKD, chronic kidney disease; CRIC, Chronic Renal Insufficiency Cohort.

Intakes of foods and beverages

Coffee

Results of the literature review suggest a lower risk of CKD for higher coffee intake. However, the evidence was not consistent, with one study showing a higher, but non-significant risk of CKD, and two studies suggesting a protective effect of coffee against CKD **(Chapter 2)**. These results for coffee are comparable to results of a previous systematic review of four population-based cohort studies with ≥6 years of follow-up (22). This review concluded that coffee drinkers had a lower incidence of CKD than non-coffee drinkers (pooled RR [95% CI] of 0.87 [0.81, 0.95]) (22). In another systematic review, a dose-response analysis was performed based on three studies. The authors reported that coffee consumption of ≥1 cup/day or ≥2 cups/day vs no intake was associated with lower incidence of CKD, and the beneficial association was more pronounced in those who consumed ≥2 cups/day vs no intake (23). However, findings of this latter systematic review have been criticised, since also cross-sectional studies were included in the dose-response analysis of incident CKD. In an additional analysis, a lower prevalence of albuminuria for coffee drinkers vs non-coffee drinkers was reported, but this was based on two cross-sectional studies only (23). In a large Mendelian randomisation (MR) study conducted with data of UK Biobank and the CKDGen consortium, consumption of one extra cup of coffee per day resulted in improved kidney health, with an odds ratio (OR) of 0.84 (95% CI 0.72, 0.98) for CKD and 0.81 (0.67, 0.97) for albuminuria (24).

Despite the vast majority of the literature suggesting protective effects of coffee against CKD development in the general population (22-24), some studies have also reported neutral associations (25). The latter is in line with the lack of association for eGFR and ACR in approximately 8000 participants of the RS (**Chapter 4**). In the larger Lifelines Cohort Study, I observed beneficial associations between higher coffee intake and annual eGFR decline and incident CKD (**Chapter 5**). Interestingly, coffee consumption was associated with less kidney function decline among several high risk groups in both cohorts, particularly type 2 diabetes patients. Results of the Lifelines Cohort Study suggest that coffee may also prevent CKD in a subgroup of CVD patients, although this was not supported by results for coffee in the Alpha Omega Cohort (β per 1 SD (~300 g/d) higher coffee consumption of -0.12 [95% CI -0.30,0.05]). The results in subgroups of diabetes patients were in line with a subgroup analysis of the Fourth Korea National health and Nutrition Examination Survey (26), and with results of the Fukuoka Diabetes Registry (27). These beneficial results among these specific subgroups may be explained by protective effects of anti-inflammatory and anti-oxidative coffee compounds (28, 29). Diabetes patients typically have higher inflammation levels than healthy participants (30), and thus these patients may in theory benefit more from drinking coffee than healthy individuals. Further research is needed to identify the specific coffee compound responsible for the beneficial effects on kidney function parameters. Another important hypothesis could be related to physical activity and/or increased energy metabolism. A recent intervention study showed that coffee consumers were more physically active than non-coffee consumers

(31). Another study also suggested a relationship of coffee with physical activity (32). Other potential mechanisms of action could be related to hepatic fat (33), but a recent trial found that supplementation with main coffee components did not attenuate hepatic fat in patients with diabetes and NAFLD (34).

Sugar added to coffee may potentially be harmful, especially for type 2 diabetes patients with poor glycaemic control. However, beneficial associations of coffee with kidney function were also found in type 2 diabetes patients of the Fukuoka Diabetes Registry who added sugar to coffee (27), suggesting that a beneficial effect of coffee is not attenuated by adding sugar. Such studies are lacking in Western diabetic patients who on average drink more coffee than Asian patients. Also the type of coffee (filtered or unfiltered) matters, but this is often not measured in FFQs, especially not in older cohorts. Cafestol in unfiltered coffee increases LDL-cholesterol levels (35). Therefore, the Dutch Health Council recommends replacing unfiltered coffee with filtered coffee in guidelines for the general population (36) and CVD patients (37). In **Chapter 3**, I omitted the coffee component from the DHD-CVD index, because type of coffee (filtered or unfiltered) was not assessed in the Alpha Omega Cohort. However, based on Dutch coffee drinking habits, I assume that most coffee was filtered in this older Dutch cohort at the time of baseline examination (2002-2006).

Insights from this thesis Consumption of (caffeinated, filtered) coffee may prevent kidney function decline in general populations, especially in those with type 2 diabetes. Before implementing coffee consumption as dietary advice for further prevention of kidney function decline in type 2 diabetes patients, it is necessary to replicate my findings in Western cohorts of diabetes patients.

Dairy

In **Chapter 2**, indications of improved kidney function were observed associated with higher intake of low-fat dairy in healthy populations. Previous research showed inconsistent results. A review of population-based studies suggested improved kidney function parameters from higher intake of low-fat dairy (38), but a recent population-based study which focused on total dairy intake and different dairy products, observed no such association for low-fat dairy intake (39). Generally, beneficial results for low-fat dairy may partly be explained by the presence of blood pressure lowering minerals (i.e., potassium, magnesium and calcium) (40). Dairy may also exert anti-inflammatory effects (41), and improve insulin sensitivity, thereby lowering the risk of type 2 diabetes (42). In CVD patients of the Alpha Omega Cohort (**Chapter 3**), however, I observed an indication of more kidney function decline in patients with higher adherence scores for the dairy guideline. Higher absolute dairy intake was especially adversely associated among patients who already had CKD at baseline. The dietary guideline for dairy does not distinguish between low-fat and full-fat dairy products, neither does it give recommendations for specific dairy products. In **Chapter 6**, I analysed the association between several dairy

products and kidney function decline in CVD patients. Yoghurt is often considered part of a healthy diet and associated with a lower risk of various cardiometabolic diseases, possibly through beneficial effects on the gut microbiome (43). Yet, I found that higher intake of plain yoghurt (irrespective of fat content) was associated with more kidney function decline. This might be explained as follows: in **Chapter 3**, the highest adherence score for dairy could only be obtained if milk or yoghurt products were consumed, as specified in the guideline for dairy. Thus the findings for adherence to dietary guidelines for dairy in **Chapter 3**, may be driven by yoghurt, which was inversely associated with kidney function decline in **Chapter 6**. Other explanations for these discrepant findings could be related to drug treatment in the Alpha Omega Cohort, which may have interfered with the effect of dairy on kidney function, resulting in contrasting associations compared to those found in the general population. Adverse effects have also been attributed to animal protein (44), but dairy protein was not associated with kidney function decline in a previous analysis of the Alpha Omega Cohort (44). Among CKD patients, however, protein has been associated with CKD progression and glomerular hyperfiltration (45), and could therefore explain the deteriorated kidney function as a result of higher dairy intake. Finally, dairy is high in phosphorus, and high dairy intake may lead to hyperphosphatemia in patients with CKD, which could result in detrimental effects on kidney function (46). My findings for dairy, including yoghurt, need replication in other cohorts and intervention studies of CVD patients with kidney function as the primary outcome.

Insights from this thesis Dairy consumption, particularly low-fat dairy, may reduce kidney function decline in apparently healthy populations, but more research is warranted given the inconsistencies observed in literature. In CVD patients, dairy intake does not seem to protect against kidney function decline, and I even found adverse associations for yoghurt. Replication of these findings is required in other CVD patient cohorts and intervention studies.

Other foods and beverages

Higher intake of red and processed meat in **Chapter 2** was associated with a higher risk of CKD in two population-based prospective cohort studies. These findings are in line with a previous population-based study, which reported a 1.4-fold higher risk of kidney failure in the top vs bottom quartile of red meat intake after 15.5 years of follow-up (47). In other population-based studies, higher red (processed) meat intake was associated with higher incidence of coronary heart disease (CHD) (48) and type 2 diabetes (49). Red (processed) meat contains animal protein, which has been linked with accelerated kidney function decline in the Alpha Omega Cohort (44). This is in line with my finding that a higher adherence score for limiting red meat intake was associated with less kidney function decline in CVD patients with a low red meat intake (**Chapter 3**). Although my results warrant replication in other CVD patient cohorts with a larger variation in red meat intake, this thesis suggests that limiting the intake

of red meat could be an important strategy for delaying kidney function decline in general populations and in CVD patients.

Nuts are often part of a healthy diet. In the National Health and Nutrition Examination Surveys (NHANES), nut consumption 1-6 times per week was associated with a lower prevalence of CKD compared to no nut consumption (50). In the same study, a lower risk of all-cause mortality was observed, which was similar for CKD patients and non-CKD patients (50). Population-based prospective studies of nut consumption and kidney function are limited. In my literature review, I observed improved kidney function parameters for higher nut intake, though based on only one study (**Chapter 2**). My findings are generally in line with findings from population-based studies that suggest a beneficial role for nuts in cardiometabolic health (51-54). In CVD patients with a low daily nut intake (~6 g/d), inconsistent results were shown for analyses with a higher adherence score (beneficial association) and absolute intake (no association) (**Chapter 3**). I could not adjust for salt intake through nuts, and my results should be interpreted with caution. Before drawing conclusions, further research is required in CVD patient cohorts with a wider range in quantity and variety of nut intake.

Legumes are considered part of a healthy diet, with beneficial effects on cardiometabolic health (55-58), although also null effects have been observed in a cross-over study (59). My observation that higher intake of legumes was associated with lower CKD risk in my literature review (**Chapter 2**) was based on one study (60). However, the results of this single study may be questioned, because not all analyses that were performed support this conclusion (60). In the Alpha Omega Cohort with a low intake of legumes among consumers (<10 g/d), a higher adherence score for sufficient legumes intake was associated with more kidney function decline (**Chapter 3**). This association was also present in patients with diabetes or obesity. In my study, included foods were mainly canned beans and capuchins, where salt may have been added. Although sodium intake is an established risk factor of CKD in general populations (61, 62), I did not find an association with kidney function decline in CVD patients (**Chapter 3**). This could be attributed to the FFQ that I used in my study, which only estimated sodium from foods, likely leading to underestimation and no association. The inconsistent results for legumes in population-based studies and CVD patients in this thesis require replication in other population-based and CVD patient cohorts.

In my literature review, I found that tea consumption was not associated with kidney function (**Chapter 2**). In literature, findings for tea are mixed. A 2-week intervention study among healthy Japanese adults reported no effect of green tea on eGFR (63). A recent MR study that used data of UK Biobank and CKDGen consortium, found that higher tea intake may be causally associated with a lower risk of CKD and albuminuria, and higher eGFR (64). The protective effects of tea on kidney health parameters may result from tea catechins, which could increase antioxidant activity (65). My neutral finding in **Chapter 2** may be due to residual

confounding, which was not present in the respective MR study (64). Dutch dietary guidelines for the general population and CVD patients encourage black or green tea consumption (36, 37). However, higher absolute intake of tea was adversely associated with kidney function decline in the Alpha Omega Cohort, particularly in a subgroup of obese patients (**Chapter 3**). Although similar studies in CVD patients are missing, my results are in line with results of the PREDIMED-Plus study of elderly participants with metabolic syndrome, which also observed more kidney function decline in tea consumers (66). The authors of this study hypothesised that caffeine from tea could have caused the accelerated kidney function decline (66). Another theory is related to the formation of kidney stones (67, 68), which may have adversely impacted the risk of CKD in (obese) CVD patients. More research into health effects from tea on parameters of kidney function in general populations and (obese) CVD patients are required.

My literature review suggests that higher intake of vegetables is associated with lower CKD risk (**Chapter 2**), though based on only two population-based studies. This finding is in agreement with a recent cross-sectional analysis and MR study in the UK Biobank (69). Other studies also suggest that a diet rich in vegetables is associated with improved kidney function (70, 71). Mechanisms that might explain the beneficial associations could be related to low acid load of vegetable-rich diets. Indeed, a recent study in patients with metabolic syndrome suggested that diets with a high acid load may contribute to kidney function impairment (72). In the Alpha Omega Cohort, however, both adherence (score) and higher absolute intake of vegetables (grams/day) were not associated with kidney function decline (**Chapter 3**).

SSBs are considered part of an unhealthy diet, with adverse effects on cardiometabolic health (73). A trend towards higher risk of CKD was observed for higher intake of SSBs in my literature review (**Chapter 2**). This result is in agreement with results of a more recent systematic review and dose-response meta-analysis of 12 prospective population-based studies, which also reported an adverse, but non-significant, association between higher intake of SSBs and CKD risk (74). In light of the evidence on SSBs and (cardiometabolic) health outcomes, the Dutch Health Council recommended lower intakes of SSBs and fruit juices for CVD patients (37). In post-MI patients, better adherence to the guidelines for limiting SSBs and fruit juices was not associated with kidney function decline (**Chapter 3**). It should be noted, however, that habitual intake of SSBs and fruit juices combined in the Alpha Omega Cohort was low (~160 g/d). More research is warranted in CVD patients with a larger variation in SSB intake.

Insights from this thesis In apparently healthy populations, limiting red meat intake is important for maintaining kidney health. In CVD patients, lowering red meat intake to a maximum of 45 g/d may slow down kidney function decline. In generally healthy populations and CVD patients, sufficient nut intake may slow down kidney function decline, but more research is warranted, given the lack of comparable studies. Legumes consumption may also prevent kidney function decline in generally healthy participants, but this may not be the case in CVD patients for whom I even found adverse associations. These contradictive findings require further investigation. This thesis showed that in healthy participants, tea may not improve nor deteriorate kidney function. However, tea may be associated with kidney function loss in CVD patients, especially in obese patients. More research in type of tea and amount is needed. Lowering SSB intake is potentially important for CKD prevention in apparently healthy individuals. For CVD patients, SSBs and fruit juices may not be as important for CKD prevention as it might be for apparently healthy individuals.

Blood biomarkers

Plasma linoleic acid

Plasma LA, mainly derived from vegetable oils, but also from nuts and seeds, has been considered as a biomarker of polyunsaturated fatty acid (PUFA) intake (75). In well-treated post-MI patients, plasma LA was only weakly correlated with LA intake (correlations <0.2), which was possibly influenced by statin use and/or alcohol use (76). Therefore, findings of plasma LA in MI patients may not be merely translated to LA intake. Another analysis of the Alpha Omega Cohort observed lower diabetes risk (HR of 0.44 [95% CI 0.26-0.75]) for patients with high (Q5, 54.3-67.6% of total FAs) vs low (Q1, 28.5-46.1% of total FAs) plasma LA levels, but no association was found for dietary LA (77). These findings are in line with my results, wherein I observed that high (>47%) vs low (≤47%) levels of plasma LA in CE were associated with 40% less kidney function decline, particularly in patients with diabetes or CKD (**Chapter 7**). My results reinforce the hypothesis that hepatic fat dysregulation, which is observed in patients with NAFLD, may play a role. This hypothesis is strengthened by accumulating evidence for a link between NAFLD and CKD in various population-based studies (78-80), including evidence for a strong cross-sectional link between NAFLD and CKD in this thesis (**Chapter 8**). The evidence on associations between plasma LA, NAFLD, diabetes, and CKD risk in mainly the Alpha Omega Cohort is summarised in **Fig. 1** below.

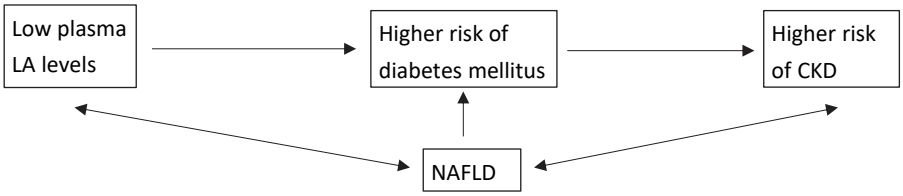


Fig. 1 Summary of observed associations between low plasma LA levels and CKD risk in mainly the Alpha Omega Cohort. In this thesis, low levels of plasma LA were found to be a predictor of accelerated kidney function decline after myocardial infarction, particularly in patients with diabetes and CKD. Further evidence showed that low plasma LA levels were associated with higher risk of diabetes in the same cohort. NAFLD may likely play a role in this association, since (i) NAFLD patients generally have lower levels of plasma LA, (ii) NAFLD was a strong predictor of diabetes risk (81), and (iii) NAFLD was cross-sectionally associated with CKD risk in the Alpha Omega Cohort. LA, linoleic acid; CKD, chronic kidney disease; NAFLD, non-alcoholic fatty liver disease.

Plasma eicosapentaenoic acid and docosahexaenoic acid

In post-MI patients, plasma EPA+DHA in CE was not a predictor of kidney function decline (**Chapter 7**), which contradicts a previous analysis of the Alpha Omega Trial where a 30% reduction in kidney function decline was observed after 40 months of supplemental EPA+DHA intake (400 mg/day) (82). I therefore hypothesise that higher dosages of EPA and DHA are needed to exert an effect. EPA and DHA are biomarkers of (fatty) fish intake (75), also in the Alpha Omega Cohort (76). Another Alpha Omega Cohort analysis showed that higher circulating and dietary EPA+DHA were associated with lower risk of (CHD) mortality after >12 years follow-up, despite a low habitual intake (83). In a pooled analysis of 25,570 individuals from 19 cohorts, higher levels of seafood derived omega-3 FAs were associated with less kidney function decline in various lipid fractions (84). However, the pooled RR of plasma EPA+DHA+DPA in CE specifically (n=3 participating cohorts), was non-statistically significant (84). Possibly, the type of lipid fraction in which EPA+DHA is measured plays a role. Unfortunately, I was not able to investigate this, because in the subgroup of patients for whom we analysed total plasma or phospholipids, data on eGFR were not available. To conclude, results on plasma EPA+DHA in relation to kidney function and (CVD) mortality in the Alpha Omega Cohort are largely inconsistent. Therefore, the role of circulating EPA+DHA on kidney function decline should be investigated further in other CVD patient cohorts with higher fish intake.

Odd-chain fatty acids and myristic acid

OCFAs (C15:0 and C17:0) and myristic acid (C14:0) measured in CE were also not a predictor of kidney function decline after MI (**Chapter 7**). OCFAs were previously related to dairy and fibre intake in the Alpha Omega Cohort (85). C14:0 has also been proposed as biomarker of dairy intake, but it also reflects saturated fat from coconut or palm oil. To my knowledge, other studies that investigate the link between circulating OCFAs and C14:0 with kidney function are lacking, and repetition of my findings in other CVD cohorts is warranted.

Insights from this thesis In clinical practice, plasma LA may be a novel biomarker for detecting accelerated kidney function decline after MI. This thesis further showed that plasma EPA+DHA, OCFAs, and C14:0 were not associated with kidney function decline in CVD patients. The inconsistent results for plasma EPA+DHA in relation to different cardiometabolic health outcomes in CVD patients, require further research in CVD patient cohorts with higher fish intake. The lack of comparative studies on OCFAs and C14:0 in relation to kidney function decline, warrant replication in other studies.

Serum uric acid

SUA is the end-product of purine metabolism, produced by the liver and primarily excreted by the kidneys (86). Thus, higher levels of SUA might be indicative of impaired kidney function and NAFLD. In **Chapter 8**, high SUA concentration was indeed cross-sectionally associated with high FLI and low eGFR. SUA (>0.50 mmol/L) as predictor of NAFLD and CKD (combined), was in turn associated with a >2-fold higher risk of (CVD) mortality. SUA in relation to mortality risk is a popular topic of investigation, with some observational studies suggesting a U-shape association (87, 88) and some a J-shape association (89). Despite its popularity, only one such study had been performed in post-MI patients. This study showed a 1.40-fold higher risk of CVD mortality for patients with SUA levels >0.38 vs <0.25 mmol/L (90). However, this study did not take NAFLD and CKD into account, and post-MI patients were less-well treated than patients in the Alpha Omega Cohort. In light of total evidence in post-MI patients, my results further highlight the potential that SUA reflects an advanced stage of cardiometabolic disorders. This may provide opportunities for more accurate risk assessment in clinical practice. For example, 60% of the patients in the Alpha Omega Cohort had NAFLD (predicted by FLI), and NAFLD was associated with CKD. Although FLI is not the gold standard to predict NAFLD in clinical practice, it is still a valid measure of NAFLD (91). Therefore, my results support the need for regular check-ups in CVD patients for impaired liver function and reduced kidney function. SUA could be considered for this purpose. More accurate risk assessment will most likely lead to opportunities for targeted therapy. More research is warranted as to which therapeutic interventions could further reduce the risk of CVD mortality.

Insights from this thesis In clinical practice, SUA could be considered as an inexpensive biomarker of cardiometabolic disorders such as NAFLD and CKD.

Methodological considerations

The validity of findings in this thesis may have been affected by methodological choices related to exposure and endpoint, study design, and analytical models. This section addresses various methodological factors that pertain to the internal and external validity of the results.

Measurements of dietary intake

Nutritional epidemiology studies often rely on data obtained with FFQs for estimating habitual intake. The FFQ is a dietary assessment tool that is commonly used to estimate an individual's dietary intake over the past year or month. The FFQ typically consists of a list of foods and beverages, and participants are asked to indicate how often they consume each item (e.g. never, monthly, weekly, daily). The FFQ is a relatively simple and low-cost tool, but it comes with limitations and potential *misclassification*.

In the Alpha Omega Cohort, a 203-item FFQ was used to estimate habitual intake, which was an extended version from an original 104-item FFQ, developed to specifically estimate intakes of FAs and cholesterol (92, 93). For each food item, questions were asked about the frequency of consumption, along with questions about portion sizes. If patients reported consumption of a home-cooked food item (such as potatoes), further inquiries were made regarding the method of preparation (e.g. fried or oven-baked). The FFQ has been previously validated against dietary history and showed high reproducibility for assessing the intake of most foods, with Spearman correlations up to 0.9 (93).

In the RS (**Chapter 4**), data on habitual dietary intake, including coffee consumption, were obtained with a validated semi quantitative 170-item and 389-item FFQ. Data on coffee consumption was additionally obtained through home interviews by trained interviewers. During home interviews, participants were asked if they consumed coffee (cups/day) over the past month. In both FFQs, questions were asked about consumption and frequency of foods and beverages during the past month, including questions about preparation method. The 170-item FFQ was validated against fifteen 24 h food records and four 24 h urinary urea excretion samples in a subsample of the RS (n=80), which demonstrated high reproducibility showing Pearson's correlations up to 0.85 for nutrient intakes and a Spearman correlation for protein intake of 0.67 (94). The 389-item FFQ was previously validated against a 9-day dietary record (95) and a 4-week dietary history (92), with Pearson's correlations for different nutrient intakes ranging between 0.40 and 0.86. In the Lifelines Cohort Study (**Chapter 5**), a self-administered 110-item FFQ was used, which was externally validated within Nutrition Questionnaires plus (NQ-plus) study. Also here, high reproducibility was observed with a Spearman correlation coefficient of 0.72 for coffee intake (96). In this FFQ, similar types of questions were asked about consumption of foods and beverages, frequency, and preparation method as in the FFQs used in the RS.

An important limitation of FFQs is *misclassification*, which could be both non-differential and differential in the cohorts described in this thesis. Non-differential misclassification may have yielded underestimated results for the DHD-CVD components studied in **Chapter 3** and dairy products in **Chapter 6**. However, obese patients may have systematically underreported unhealthy foods, and overreported healthy foods (97), likely leading to differential

misclassification. As a result, associations in **Chapter 3** for healthy foods (legumes, nuts, dairy, and tea) may have been overestimated in subgroups of obese patients, and underestimated for unhealthy foods (red meat and alcohol). Similarly in **Chapter 6**, associations for cheese and dairy desserts in obese patients may have been underestimated, and overestimated for milk and yoghurt. Despite the possibility of misclassification, the reported intakes of individual DHD-CVD components (**Chapter 3**) and dairy products (**Chapter 6**) of most post-MI patients were comparable with results of detailed food records obtained from the general elderly Dutch population (98). In the RS and Lifelines Cohort Study, misclassification of self-reported coffee consumption is expected to be low. This is due to coffee consumption being a long-standing lifestyle habit, which allows individuals to better memorise their actual coffee intake. Consequently, this may have led to more accurate associations for coffee consumption in **Chapters 4** and **5**.

In this thesis, single measurements of baseline dietary intake were examined in relation to kidney function parameters. The average baseline age of post-MI patients in the Alpha Omega Cohort and healthy participants in the RS was comparable (around 67 years) and dietary habits have been reported to be less likely to change over time at older age (99). However, coffee consumption frequency in the RS and the Lifelines Cohort Study may have changed in participants who developed a chronic disease during the course of the study, and I observed the strongest associations in people with chronic diseases in **Chapters 4** and **5**. In the Lifelines Cohort Study, I observed strong beneficial associations in all participants. I cannot completely rule out the possibility that participants with a chronic disease at baseline may have changed their coffee consumption habits over time. However, results on coffee consumption in this thesis and a previous study in diabetes patients (27), support the notion that changes in coffee consumption over time due to chronic disease development, probably did not affect the (beneficial) associations that I observed (overall and in high risk subgroups) in the RS and Lifelines Cohort Study.

Misclassification of dietary intake is an important limitation of the FFQs that were used in the cohorts described in this thesis. Non-differential misclassification is present, which may have led to attenuated associations of DHD-CVD components and dairy products. Differential misclassification is likely present in obese individuals, which may have resulted in overestimated associations for healthy foods (legumes, nuts, dairy, and tea), and diluted associations for unhealthy foods (red meat and alcohol). For coffee consumption, generally a long-term habit, misclassification and subsequent dilution of the associations was less likely to be a problem.

Measurements of blood biomarkers

In cohort studies, plasma FAs are often expressed as relative concentrations (% of total FAs) rather than absolute levels, which yields stronger correlations with dietary FA intakes (100, 101). Results of FAs in CE in this thesis are therefore expressed in relative concentrations, as was also the case in previous analyses in the Alpha Omega Cohort on circulating FAs (76, 77, 83, 85) (**Chapter 7**).

I used a single measurement of plasma FAs in the research described in this thesis. FA composition of plasma fractions are considered to reflect short-term intake (a few weeks), but a study of Ma et al. (102) suggested that circulating FAs may also be used to reflect longer-term intake. This study further supports the use of a single baseline measurement of plasma FAs in the Alpha Omega Cohort.

SUA (**Chapter 8**) was measured using a standard immunoassay from Roche diagnostics, and the measurements were reliable with inter- and intra-coefficients of variation <10%.

Assessment of kidney function

eGFR is a valid measure of kidney function in clinical practice and often used in epidemiological studies. True GFR can be measured using inulin (the gold standard), but this method is not preferred in clinical practice, because of the invasiveness for the patient (103, 104). Instead, several equations have been developed over time to estimate GFR. The MDRD study equation with either six (105) or four variables (106), was developed in patients with established CKD, but may underestimate GFR in individuals without CKD (9). Therefore, I did not use this equation in this thesis. To overcome this limitation, the CKD-EPI equation was developed in CKD patient cohorts and population-based cohorts (107), and it provides a more accurate eGFR in non-CKD populations. I decided to use the combined creatinine-cystatin C based CKD-EPI equation in all Alpha Omega Cohort studies, because research showed that the combined equation is more accurate than either of the markers alone (108). In the RS and the Lifelines Cohort Study, I used the creatinine-based CKD-EPI equation, because data availability on cystatin C was too limited. A methodological problem for eGFR assessment is related to serum creatinine. Serum creatinine is a waste product, resulting from muscle breakdown, which is likely present in the elderly or patients with a chronic disease.

Alpha Omega Cohort patients in this thesis are aged 60-80 years and have been diagnosed with CVD. Therefore, these MI patients suffer most likely from muscle loss, have lower levels of creatinine in blood, and have consequently less accurate eGFR values than younger healthy individuals. Since this occurs in all MI patients, non-differential misclassification of eGFR is likely present in all Alpha Omega Cohort analyses (**Chapters 3, 6, 7 and 8**), which may have led to imprecise estimates with wider CIs. RS participants (**Chapter 4**) had a similar average age as MI patients, but were generally healthy. Lifelines Cohort Study participants (**Chapter**

5) were younger than RS participants (~46 years), and also apparently healthy. Also here, misclassification of eGFR is likely non-differential, because both cohorts have a prospective design.

Recently, the CKD-EPI Collaboration constructed a new equation without the race variable to estimate GFR (109). Although 99% of patients in the Alpha Omega Cohort is Caucasian, and applying this new equation to Alpha Omega Cohort data would be of less concern, I decided to use this recently developed combined CKD-EPI equation in **Chapters 3, 6, and 8**. In **Chapter 7**, I calculated eGFR using the CKD-EPI equation with the race variable, and CKD prevalence was 17%. The CKD prevalence was considerably lower if I calculated eGFR using the CKD-EPI equation without race (**Chapters 3, 6, and 8**), also in line with this editorial from Gansevoort et al. (110).

Generally, serum creatinine can be measured via the modified kinetic Jaffé method or an enzymatic method. The Jaffé method is a valid method used in labs for the measurement of serum creatinine, because of its low costs. However, this method is also more prone to errors (111). In Alpha Omega Cohort, serum creatinine was measured with the modified kinetic Jaffé method, although data on enzymatically measured serum creatinine was also available. The choice of using the modified kinetic Jaffé method was in line with previous Alpha Omega Cohort studies of kidney function (44, 82, 112-114). The choice of using the Jaffé method to measure creatinine in blood may have resulted in less accurate estimates of GFR, and non-differential misclassification of CKD. In the RS and the Lifelines Cohort Study (**Chapters 4** and **5**), serum creatinine was measured with the more specific enzymatic method, likely leading to more accurate GFR estimates.

KDIGO 2012 clinical practice guidelines recommend to estimate a patient's GFR at least twice within three months if there is an indication of CKD (10). However, eGFR was assessed only once in this thesis, thus it is uncertain whether patients with eGFR <60 mL/min per 1.73 m^2 really had CKD. The single measurement of eGFR may have led to misclassification of CKD diagnoses, but this was likely non-differential, and may have led to imprecise hazard ratios with wider CIs for incident CKD in **Chapters 4** and **5**. Additional data on measurements of albuminuria could have helped in correctly classifying patients with CKD. Unfortunately, urine samples were not collected in the Alpha Omega Cohort and the Lifelines Cohort Study. In the RS, urine samples were collected, and I did an additional analysis with data on albuminuria using the ACR in **Chapter 4**. Results for ACR were in line with results for eGFR.

In this thesis, **misclassification of eGFR or CKD** likely occurred in the various cohorts. The misclassification is non-differential, because all studies had a prospective design and knowing the exposure cannot affect the measurement of eGFR or CKD. The non-differential misclassification likely led to imprecise estimates with wider CIs in Chapters 2-8.

Selection bias, reverse causation bias, and confounding

Selection bias is a potential source of bias in prospective cohort studies, especially if there is differential loss to follow-up. In the Alpha Omega Cohort, only one patient was lost to follow-up, making *selection bias* unlikely. In the RS, persons aged ≥45 years and living in the Ommoord district of Rotterdam were invited to participate in the study. The response rate was relatively high (72%) and follow-up was almost complete. Non-random dropout of participants with a low kidney function may have occurred, but a previous analysis in the RS showed that only 0.3% of participants were on dialysis or received a kidney transplant at some point during follow-up (115). In the Lifelines Cohort Study, participants were recruited via their general practitioner, participating family members, or online self-registration (116). In a previous study performed by Klijs et al. (117), the risk of selection bias was evaluated, by investigating representativeness of the adult study population and differences in study population according to recruitment strategy. Results suggested a low risk of selection bias, because the Lifelines adult study population was found broadly representative for the adult population of north of the Netherlands, and the recruitment strategies used had only a minor effect on the level of representativeness (117).

Reverse causation bias, which hampers the causal interpretation of identified associations, is a major concern in cross-sectional studies. However, reverse causation could also be a problem in longitudinal studies. Researchers generally try to account for this by excluding the first two or three years of follow-up in data-analyses. I could not perform this type of sensitivity analysis in this thesis, due to relatively short follow-up duration of the Alpha Omega Cohort (~3.4 years), the RS (~5.4 years), and the Lifelines Cohort Study (~3.6 years).

Despite adjustment for a wide range of dietary and lifestyle factors and medication use in all studies presented in this thesis, *residual confounding* can still be a concern. For example, FFQs used in this thesis were not appropriate for measuring salt intake, since only salt from foods was calculated and because the salt content can vary significantly depending on the brand of the product. Salt represents a major risk factor for kidney function decline and consumption can be linked to various food items. For example, in the DHD-CVD index, guidelines recommend to consume unsalted nuts, but the FFQs used in this thesis do not distinguish between salted and unsalted nut consumption. Also, salt added to red meat may have confounded associations with kidney function decline. Consequently, total salt intake

is underestimated, and this could have weakened the associations of red meat (and other foods where people tend to add salt) with kidney function decline.

Selection bias was unlikely to be a major problem in the Alpha Omega Cohort, the RS, and the Lifelines Cohort Study. Although I adjusted for a wide range of confounders in my studies, **residual confounding** by salt intake cannot be fully excluded.

External validity

In the Alpha Omega Cohort of well-treated post-MI patients, disease state could have influenced dietary intake. Furthermore, CVD patients may already have an altered FA profile (118), possibly induced by medication use, the presence of cardiometabolic risk factors, and the underlying disease process. For these reasons, results may not be generalisable to healthy populations. However, results could still pertain to high risk populations, such as those with hyperlipidaemia, hypertension, and type 2 diabetes. Results of the RS and the Lifelines Cohort Study are generalisable to general populations, but less generalisable to different ethnic groups (this also applies to the Alpha Omega Cohort). Furthermore, individuals with higher socioeconomic status (SES) tend to eat healthier than the ones with lower SES, and they are usually more likely to participate in studies. However, in the Alpha Omega Cohort, the majority of patients had a low education level **(Chapter 3)**. In the Lifelines Cohort Study, ~40% of participants had an intermediate education level, and 31% was highly educated (**Chapter 4**). Similar proportions were observed in the RS **(Chapter 3)**. Therefore, I think my results are also generalisable to low SES individuals. Finally, analyses in women in the Alpha Omega Cohort were underpowered (only ~20% was female), likely leading to less precise estimates and associations with wider CIs. Therefore, extrapolation of findings to female CVD patients should be done with caution. This was likely not a problem in the RS and Lifelines Cohort Study, where men and women were more evenly distributed in the cohorts (~58% women in both cohorts). In general, analyses in patients with diabetes, obesity, CKD, and other high risk groups, were also underpowered in this thesis, because of small sample size. Caution is needed when extrapolating these results to diabetes, obesity, and CKD patients.

Directions for future research and clinical implications

This thesis highlights various research needs, which are listed below.

1. Defining the preferred dietary pattern for CKD prevention in CVD patients.

This thesis showed that the DASH diet and Mediterranean diet were consistently associated with improved kidney function parameters in apparently healthy populations. In CHD patients of the CORDIOPREV trial, the consumption of a Mediterranean diet was more effective in reducing kidney function decline than a low-fat diet after five years of follow-up. However, the DHD-CVD index designed for CVD patients was not associated with kidney function decline in this thesis. Evidently, the dietary factors and thresholds used to define the DHD-CVD score may not have sufficiently captured the optimal diet for slowing down kidney function decline in CVD patients. Future studies should address this knowledge gap in a cohort of CVD patients who are largely treated with cardiovascular and lipid-lowering medication.

2. Studying (types of) coffee consumption in relation to kidney function in patients with type 2 diabetes, including elucidation of potential underlying mechanisms.

This thesis showed that coffee consumption was associated with improved kidney function parameters, especially in type 2 diabetes patients. However, potential underlying mechanisms remain unknown. Only one similar study on coffee and kidney function so far has been performed in diabetics. Therefore, future research should focus on the relationship between coffee consumption and kidney function parameters specifically in diabetics, and also investigate potential underlying mechanisms. Effects of coffee on kidney function may differ depending on type of coffee consumption (e.g. filtered or unfiltered) and additives used (milk, sugar and artificial sweeteners). Therefore, FFQs that are used to measure coffee consumption should ideally also include questions about type of coffee consumption, and types of additives used.

3. Studying dairy products in relation to kidney function in other CVD patient cohorts.

In this thesis, milk, hard cheeses and dairy desserts were not associated with kidney function decline after MI, whereas an unexpected adverse association was observed for yoghurt (irrespective of fat content). Replication in other cohorts of CVD patients is required, particularly for yoghurt. A MR study in CVD patients of European ancestry could help in answering the question whether the observed association is causal. Metabolomics and gut microbiome studies could provide insight in potential pathways for the adverse association of yoghurt. Similarly, studies on OCFAs (C15:0 and C17:0, biomarkers of dairy intake) and kidney function in CVD patients are lacking, and my null findings warrant confirmation. If results on

OCFAs are confirmed, OCFAs can probably not be used as novel biomarker to detect patients at high risk of CKD in clinical practice.

4. Understanding differences in the relation of circulating EPA+DHA vs supplemental EPA+DHA intake with kidney function decline.

Post-MI patients who received 400 mg/d of supplemental EPA+DHA intake for ~40 months, had 2.1 mL/min per 1.73 m^2 (95% CI 0.6-3.6) less kidney function decline than the placebo group. However, this thesis showed no association for circulating EPA+DHA with kidney function decline after MI. I hypothesise that a higher dosage of EPA+DHA on top of habitual dietary intake in the Dutch population is needed to exert an effect.

5. Exploring the role of the liver in the association of plasma LA in CE and kidney function parameters in CVD patients.

In this thesis, plasma LA was associated with 40% less kidney function decline after MI, particularly in patients with diabetes and CKD. Plasma LA was also previously associated with lower incidence of diabetes in the Alpha Omega Cohort. I hypothesise that NAFLD could play a role in this association. Further research on this hypothesis in the Alpha Omega Cohort and other CVD patient cohorts is required.

Implications for research and clinical practice

This thesis yielded new insights for research and has possible implications for clinical practice, which are outlined below.

- Coffee consumption may fit into a healthy diet to delay kidney function decline and consumption could be especially promoted among type 2 diabetes patients.

- Low levels of plasma LA (<47% of total FAs) could be used as biomarker to identify CVD patients at risk of CKD.

- In clinical practice, SUA could be considered as an inexpensive biomarker to examine CVD patients for the combined occurrence of fatty liver and impaired kidney function.

- The optimal diet for delaying kidney function decline in general populations may not be effective in CVD patients. Of all studied DHD-CVD components, only limiting red meat intake to ≤45 g/d was identified as a useful guideline for CKD prevention in CVD patients.

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Appendices

Summary | Samenvatting

Acknowledgements | Dankwoord

About the author

Summary

English summary

Nederlandse samenvatting

Chronic kidney disease (CKD) has become a major problem worldwide, with a global prevalence of 9% and 1.2 million deaths in 2017. CKD is a progressive condition characterised by a gradual kidney function decline over time. Kidney function is often estimated using the glomerular filtration rate (eGFR, in mL/min per 1.73 m^2), and CKD is then defined as eGFR <60 mL/min per 1.73 m^2 for at least three months. Albuminuria is an indicator of kidney damage, which is measured by urinary albumin-to-creatinine ratio (ACR). Kidney function declines with on average 1.0 mL/min per 1.73 m^2 per year, probably starting in someone's mid-thirties. Cardiovascular disease (CVD) patients have accelerated kidney function decline, which makes these patients more prone to develop CKD. CKD and CVD share common risk factors, such as diabetes, hypertension, obesity, smoking, and poor diet. A healthy lifestyle, including a healthy diet, is important for lowering the risk of CVD, and thus may also help to slow down kidney function decline in CVD patients. Adopting a healthier lifestyle is often used as treatment in patients with non-alcoholic fatty liver disease (NAFLD), a term used to describe a range of liver conditions that are unrelated to excessive alcohol intake. NAFLD is strongly linked to obesity, type 2 diabetes, CKD, and CVD. Therefore, it is of interest to also study the relationship of NAFLD and CKD in CVD patients.

The main objective of this thesis was to investigate associations of nutritional factors with kidney function decline in general populations and cardiovascular patients. I first examined dietary intake and diet quality in relation to kidney function decline (**Chapters 2 and 3**). I then focused on coffee consumption (**Chapters 4 and 5**) and dairy products (**Chapter 6**), because their role in slowing down kidney function decline is less clear. In the final part, I investigated on blood biomarkers. Plasma fatty acids (FAs) as potential predictor of accelerated kidney function decline were examined in **Chapter 7.** Serum uric acid (SUA) may be used as alternative indicator of CKD, since uric acid is mainly excreted by well-functioning kidneys. In **Chapter 8**, serum uric acid (SUA) was examined in relation to NAFLD and CKD, and subsequently linked to risk of (CVD) mortality. I analysed data of over 2000 drug-treated Dutch CVD patients of the Alpha Omega Cohort aged 60-80 years (~80% male) with a myocardial infarction (MI) up to 10 years before study enrolment. Additionally, data were analysed of over 7500 Rotterdam Study (RS) participants (mean age 66 years) and over 78,000 Lifelines Cohort Study participants (mean age 45 years) – both population-based cohorts.

In **Chapter 2**, I performed a literature review of population-based studies with a follow-up of ≥3 years, studying associations of dietary patterns and intake of commonly consumed foods and beverages with incident CKD. I found convincing evidence that healthy dietary patterns (i.e., Mediterranean diet, Dietary Approaches to Stop Hypertension (DASH) diet) may lower CKD risk (RR <0.90). The evidence for intake of individual foods and beverages in relation to CKD was more variable and weaker. Coffee and low-fat dairy intake were mainly beneficial, whereas intake of red (processed) meat and sugar-sweetened beverages were associated

with more kidney function decline. No associations were observed for poultry, fermented and nitrate-containing vegetables, fruits, tea, and diet beverages.

In **Chapter 3**, the Dutch Healthy Diet Cardiovascular Disease (DHD-CVD) index as a measure of overall diet quality was calculated, using the Dutch dietary guidelines for CVD patients. I then performed a prospective analysis of the association between the DHD-CVD index and kidney function decline in Dutch post-MI patients of the Alpha Omega Cohort. I also investigated whether this association differed by genetic risk of CKD. After multivariable adjustment, overall diet quality as measured by the DHD-CVD index, was not associated with annual kidney function decline, also not in strata of genetic CKD risk. When I studied the individual DHD-CVD components, I found that higher adherence scores for limiting red meat intake and sufficient nut consumption were associated with less annual kidney function decline (β per 1-SD decrease of 0.21 [95% CI: 0.04,0.38] for red meat and β per 1-SD increment of 0.17 [-0.004,0.34] for nuts). However, higher adherence scores for legumes and dairy were associated with more annual kidney function decline (β per 1-SD increment: $-0.20_{legumes}$ [-0.37,-0.04] and -0.18_{dairy} [-0.34,-0.01]). Generally similar results were obtained in strata of genetic CKD risk. Overall, these data suggest that dietary factors and thresholds used to define the DHD-CVD index may not have captured the optimal diet for slowing down kidney function decline in CVD patients. More research is needed on preferred dietary regimens for CKD prevention in CVD.

In the literature review of population-based studies in **Chapter 2**, I observed that coffee consumption may be beneficially associated with incidence of CKD. I investigated this association further in RS participants in **Chapter 4** and participants of the Lifelines Cohort Study in **Chapter 5**. Habitual coffee consumption was not associated with kidney function decline in **Chapter 4** during a median follow-up of ~5.4 years in the total study population. However, after stratification for subgroups at higher risk of CKD, I found that one additional cup of coffee per day was associated with improved kidney function among those aged >70 years and among obese individuals. A protective trend was observed among former smokers and type 2 diabetes patients. I additionally examined urinary ACR, for which I observed no association. In the bigger Lifelines Cohort Study (**Chapter 5**), I observed that one additional cup of coffee per day was associated with less kidney function decline after ~3.6 years of follow-up (β of 0.03 [95% CI: 0.02,0.04]). This beneficial association persisted in several higher risk groups, with the highest benefit observed among type 2 diabetes patients (0.10 [0.05,0.17]). Overall, my findings may suggest that coffee consumption could be important for slowing down kidney function decline, especially for diabetes patients.

Chapter 2 showed that dairy, particularly low-fat dairy, could be important for the prevention of CKD in general populations. Dairy is a heterogenous group of products, and associations with cardiometabolic diseases may differ for each product. Furthermore, studies on dairy

and different dairy products are lacking in drug-treated CVD patients. Therefore, I studied this association in more detail in post-MI patients of the Alpha Omega Cohort in **Chapter 6**. In this group, intakes of milk, hard cheeses, and dairy-based desserts were not significantly associated with kidney function after 40 months of follow-up. However, I observed an adverse association for high vs low intake of yoghurt, irrespective of fat content, which could not be further explained in various subgroup and sensitivity analyses. Continuous analyses showed no clear dose-response association. Given the lack of studies on yoghurt and kidney function in CVD patients, the results for yoghurt should be interpreted with caution.

Nutritional blood biomarkers could be used for early detection of CVD patients with accelerated kidney function decline. In **Chapter 7**, I studied whether plasma linoleic acid (LA), eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), odd chain FAs (OCFAs, C15:0 and C17:0), and C14:0 measured in cholesteryl esters, could predict kidney function decline in post-MI patients of the Alpha Omega Cohort. After controlling for confounders, I observed that high vs low plasma LA levels were associated with 40% less annual kidney function decline. This association was particularly pronounced in diabetes patients. Plasma EPA and DHA, OCFAs, and C14:0 were not associated with kidney function decline. Overall, these results may suggest that low plasma LA levels could be used to detect patients at higher risk of CKD, particularly in patients with diabetes.

In **Chapter 8**, the cross-sectional association between SUA, NAFLD and CKD was examined, and I used the fatty liver index as proxy for NAFLD. In a subsequent prospective analysis, I investigated SUA (as potential biomarker of the combined presence of NAFLD and CKD) in relation to long-term mortality risk in post-MI patients. I found that NAFLD was strongly associated with CKD (also in patients without obesity and diabetes), which was reflected by higher levels of SUA. During 12 years of follow-up, 1592 patients died of whom 713 from CVD. Compared to SUA levels >0.30-0.35 mmol/L, patients with SUA >0.35 mmol/L had a higher risk of all-cause mortality, with a hazard ratio (HR) of 2.13 (95% CI: 1.75,2.60) for patients with SUA >0.50 mmol/L. For CVD mortality, the HR was 2.43 (1.83,3.25). These associations were likely driven by the high proportion of patients with the combined presence of NAFLD and CKD. These results highlight the potential that SUA reflects an advanced stage of cardiometabolic disorders. Use of SUA as biomarker in clinical practice may provide more accurate risk assessment.

The findings of this thesis are discussed in more detail in **Chapter 9**. Furthermore, methodological considerations and suggestions for further research are provided. Healthy dietary patterns, such as the Mediterranean diet and DASH diet, likely prevent CKD in general populations, but the preferred dietary pattern for CKD prevention in CVD patients warrants further research. For implementation in dietary advice, coffee consumption could be important for prevention of CKD, particularly in type 2 diabetes patients. However, more

research is required in Western cohorts of type 2 diabetes patients. Limiting red meat intake could also be important for slowing down kidney function decline in both general populations and CVD patients. With regard to blood biomarkers, low plasma LA levels could function as indicator of accelerated kidney function decline in CVD. SUA likely reflects more advanced stages of cardiometabolic diseases, and could provide more accurate risk assessment in clinical practice. In some chapters, I found promising results for a role of nutritional factors in preventing CKD in vulnerable subgroups at higher risk of CKD. However, some of these subgroups had a small sample size (e.g. those with diabetes, obesity, CKD, and women [only in the Alpha Omega Cohort]), and caution is needed when extrapolating these results to diabetes, obesity, CKD patients, and women.

Chronische nierschade (CNS) is wereldwijd een groot probleem met een prevalentie van 9% en 1.2 miljoen doden in 2017. CNS is een progressieve ziekte dat gekenmerkt wordt door geleidelijke nierfunctiedaling over de tijd. Een maat voor nierfunctie is de glomerulaire filtratiesnelheid (eGFR, uitgedrukt in mL/min per 1.73 m^2). CNS wordt dan gedefinieerd als eGFR <60 mL/min per 1.73 m^2 voor ten minste drie maanden. Albuminurie is een indicator voor nierschade en dat wordt gemeten door de albumine-creatinine ratio (ACR) in urine. De nierfunctie daalt gemiddeld genomen met 1.0 mL/min per 1.73 m^2 per jaar in algemeen gezonde populaties en deze daling begint ongeveer als iemand 35 jaar oud is. Hart- en vaatziekten (HVZ) patiënten hebben versnelde nierfunctiedaling en dus hebben zij een hoger risico om CNS te ontwikkelen. CNS en HVZ hebben veel risico factoren gemeen, zoals diabetes, hypertensie, obesitas, roken en een ongezond voedingspatroon. Een gezonde leefstijl dat ook een gezond dieet omvat, is belangrijk voor het verlagen van het risico op HVZ en dus zou het ook kunnen helpen om nierfunctiedaling te vertragen in HVZ patiënten. Een gezondere leefstijl wordt al vaak gebruikt als behandeling voor patiënten met niet-alcoholische leververvetting (NAFLD). NAFLD is een verzamelnaam van leveraandoeningen niet veroorzaakt door overmatig alcoholgebruik. NAFLD hangt sterk samen met andere ziekten, zoals obesitas, type 2 diabetes, CNS en HVZ. Daarom is het ook interessant om de relatie tussen NAFLD en CNS in HVZ patiënten te bestuderen.

Het doel van dit proefschrift was om de samenhang tussen voedingsfactoren en nierfunctiedaling te bestuderen in algemeen gezonde populaties en HVZ patiënten. Ik heb als eerst de rol van voedingsinname en voedingskwaliteit onderzocht (**hoofdstukken 2 en 3**). Vervolgens heb ik specifiek gekeken naar koffie (**hoofdstukken 4 en 5**) en zuivelproducten (**hoofdstuk 6**), omdat de rol van deze producten op nierfunctiedaling nog niet helemaal duidelijk was. In het laatste deel heb ik de rol van bloed biomarkers onderzocht. Ik onderzocht in **hoofdstuk 7** verschillende plasma vetzuren als mogelijke voorspeller van versnelde nierfunctiedaling. Serum urinezuur zou kunnen worden gebruikt als alternatieve indicator van CNS, omdat urinezuur hoofdzakelijk wordt uitgescheiden door goed functionerende nieren. In **hoofdstuk 8** onderzocht ik serum urinezuur in relatie tot NAFLD en CNS en dit bracht ik vervolgens in verband met risico op (HVZ) sterfte. Ik heb data van meer dan 2000 Nederlandse HVZ patiënten van het Alpha Omega Cohort geanalyseerd (60-80 jaar oud, 80% man), die allemaal een myocardinfarct (MI) hebben doorgemaakt. Daarnaast heb ik ook data geanalyseerd van meer dan 7500 Rotterdam Study (RS) deelnemers (gemiddeld 66 jaar oud) en meer dan 78,000 Lifelines Cohort Study deelnemers (gemiddeld 45 jaar oud) – beide algemeen gezonde populaties.

In **hoofdstuk 2** heb ik een literatuurstudie gedaan waarin ik populatiegerichte studies met een follow-up duur van tenminste drie jaar heb geïncludeerd. Deze studies bestudeerden associaties tussen voedingspatronen, de consumptie van veelvoorkomende voedingsmiddelen en dranken en het optreden van CNS. Ik vond overtuigend bewijs dat

gezonde voedingspatronen (bijvoorbeeld het Mediterrane dieet en het DASH dieet) het risico op CNS kunnen verlagen (relatief risico <0.90). Het bewijs voor de consumptie van individuele voedingsmiddelen en dranken in relatie tot CNS was variabeler en zwakker. Koffie en magere zuivelinname waren voornamelijk gunstig geassocieerd, terwijl consumptie van rood (bewerkt) vlees en suikerhoudende dranken geassocieerd was met een grotere achteruitgang van de nierfunctie. Er werden geen verbanden gevonden voor gevogelte, gefermenteerde en nitraatrijke groenten, fruit, thee en light dranken.

In **hoofdstuk 3** werd de Dutch Healthy Diet Cardiovascular Disease (DHD-CVD) index berekend als maat voor de algehele voedingskwaliteit. Voor de berekening hiervan is gebruik gemaakt van de Nederlandse voedingsrichtlijnen voor patiënten met HVZ. Vervolgens heb ik een prospectieve analyse gedaan naar de associatie tussen de DHD-CVD index en de achteruitgang van de nierfunctie bij Nederlandse post-MI patiënten van het Alpha Omega Cohort. Ook heb ik onderzocht of deze associatie verschilde in MI patiënten met een laag, gemiddeld en hoog genetisch risico op CNS. Na correctie voor meerdere variabelen was de algehele voedingskwaliteit, gemeten door de DHD-CVD index, niet geassocieerd met de jaarlijkse achteruitgang van de nierfunctie, ook niet in subgroepen met een genetisch risico op CNS. Bij het bestuderen van de individuele componenten van de DHD-CVD index werd echter gevonden dat hogere scores voor het beperken van de consumptie van rood vlees en voldoende consumptie van noten geassocieerd waren met een lagere jaarlijkse achteruitgang van de nierfunctie (β per 1-SD afname van 0.21 [95% betrouwbaarheidsinterval: 0.04, 0.38] voor rood vlees en β per 1-SD toename van 0.17 [-0.004, 0.34] voor noten). Daarentegen waren hogere scores voor de consumptie van peulvruchten en zuivel geassocieerd met een hogere jaarlijkse achteruitgang van de nierfunctie (β per 1-SD toename: $-0.20_{\text{peulvruchten}}$ [-0.37, -0.04] en -0.18_{zuivel} [-0.34, -0.01]). Vergelijkbare resultaten werden verkregen in subgroepen met een genetisch risico op CNS. Over het geheel genomen suggereren deze gegevens dat de voedingsfactoren en afkapwaarden die zijn gebruikt om de DHD-CVD index te definiëren mogelijk niet het optimale voedingspatroon hebben vastgelegd om de achteruitgang van de nierfunctie bij HVZ patiënten te vertragen. Meer onderzoek is nodig naar het optimale voedingspatroon voor de preventie van CNS bij HVZ.

In de literatuurstudie in **hoofdstuk 2** vond ik dat koffieconsumptie mogelijk gunstig geassocieerd was met het ontstaan van CNS. Ik heb deze associatie verder onderzocht bij deelnemers van de RS in **hoofdstuk 4** en bij deelnemers van de Lifelines Cohort Studie in **hoofdstuk 5**. Koffieconsumptie was in **hoofdstuk 4** niet geassocieerd met nierfunctiedaling, gedurende een follow-up van ongeveer 5.4 jaar in de totale onderzoekspopulatie. Echter, na stratificatie voor subgroepen met een hoger risico op CNS, vond ik dat één extra kopje koffie per dag geassocieerd was met verbeterde nierfunctie bij personen ouder dan 70 jaar en bij personen met obesitas. Een beschermende trend werd waargenomen bij ex-rokers en bij patiënten met type 2 diabetes. Daarnaast heb ik gekeken naar de ACR als alternatieve

maat voor nierschade, waarvoor geen associatie werd gevonden. In de grotere Lifelines Cohort Studie (**hoofdstuk 5**) vond ik dat één extra kopje koffie per dag geassocieerd was met minder achteruitgang van de nierfunctie na ongeveer 3.6 jaar follow-up (β van 0.03 [95% betrouwbaarheidsinterval: 0.02, 0.04]). Deze gunstige associatie was ook aanwezig in verschillende risico groepen, waarbij het grootste voordeel werd waargenomen bij patiënten met type 2 diabetes (0.10 [0.05, 0.17]). Over het algemeen suggereren deze bevindingen dat koffieconsumptie mogelijk kan helpen bij het vertragen van de achteruitgang van de nierfunctie, vooral bij diabetespatiënten.

Hoofdstuk 2 toonde aan dat zuivel, met name magere zuivel, belangrijk kan zijn voor de preventie van CNS in algemeen gezonde populaties. Zuivel is een heterogene groep producten en associaties met cardiometabole ziekten kunnen verschillen voor elk product. Bovendien ontbreken studies naar zuivel en verschillende zuivelproducten bij HVZ patiënten die medicatie gebruiken. Daarom heb ik deze associatie in meer detail bestudeerd bij post-MI patiënten van het Alpha Omega Cohort in **hoofdstuk 6**. In deze groep was de consumptie van melk, harde kazen en toetjes op basis van zuivel niet significant geassocieerd met de nierfunctie na 40 maanden follow-up. Echter, een ongunstige associatie werd waargenomen voor een hoge versus lage consumptie van yoghurt, ongeacht het vetgehalte, dat niet verder kon worden verklaard in verschillende subgroep- en sensitiviteitsanalyses. Continue analyses voor yoghurt toonden geen duidelijke dosis-responsrelatie aan. Gezien het gebrek aan studies naar yoghurt en nierfunctie bij HVZ patiënten, moeten de resultaten voor yoghurt voorzichtig worden geïnterpreteerd.

Biomarkers in bloed gerelateerd aan voeding zouden kunnen worden gebruikt voor vroegtijdige detectie van HVZ patiënten met versnelde achteruitgang van de nierfunctie. In **hoofdstuk 7** heb ik onderzocht of plasma linolzuur (LA), eicosapentaeenzuur (EPA), docosahexaeenzuur (DHA), oneven keten vetzuren (C15:0 en C17:0) en C14:0 gemeten in cholesterolesters, de achteruitgang van de nierfunctie kunnen voorspellen bij post-MI patiënten van het Alpha Omega Cohort. Na correctie voor confounders bleken hoge versus lage niveaus van plasma LA geassocieerd met 40% minder jaarlijkse achteruitgang van de nierfunctie. Deze associatie was met name opvallend bij diabetespatiënten. Plasma EPA en DHA, C15:0, C17:0 en C14:0 waren niet geassocieerd met de achteruitgang van de nierfunctie. Over het algemeen suggereren deze resultaten dat lage niveaus van plasma LA gebruikt kunnen worden voor detectie van patiënten met een hoger risico op CNS, met name bij patiënten met diabetes.

In **hoofdstuk 8** werd de cross-sectionele associatie tussen serum urinezuur, NAFLD en CNS onderzocht, waarbij de index voor het hebben van een vervette lever als maat voor NAFLD werd gebruikt. In een daaropvolgende prospectieve analyse onderzocht ik de samenhang tussen serum urinezuur (als mogelijke biomarker voor de gecombineerde aanwezigheid van NAFLD en CNS) en het risico op sterfte bij post-MI patiënten. NAFLD was sterk geassocieerd

met CNS (ook bij patiënten zonder obesitas en diabetes) en de concentratie serum urinezuur weerspiegelde deze associatie. Gedurende 12 jaar follow-up overleden 1592 patiënten, waarvan 713 aan HVZ. Patiënten met serum urinezuur niveaus >0.35 mmol/L hadden een hoger risico op sterfte dan patiënten met serum urinezuur niveaus >0.30-0.35 mmol/L, met een hazard ratio (HR) van 2.13 (95% betrouwbaarheidsinterval: 1.75, 2.60) voor patiënten met serum urinezuur >0.50 mmol/L. Voor sterfte door HVZ was de HR 2.43 (1.83, 3.25). Deze associaties werden waarschijnlijk veroorzaakt door het hoge percentage patiënten met zowel NAFLD als CNS. De resultaten benadrukken de mogelijkheid van SUA om te worden gebruikt als indicator voor een verder gevorderd stadium van cardiometabole aandoeningen. Het gebruik van SUA als biomarker in de klinische praktijk zou kunnen zorgen voor een nauwkeurigere risicobeoordeling van patiënten.

De bevindingen van dit proefschrift worden uitvoerig besproken in **hoofdstuk 9**. Daarnaast worden in dit hoofdstuk methodologische overwegingen en suggesties voor toekomstig onderzoek gegeven. Gezonde voedingspatronen, zoals het Mediterrane dieet en het DASH-dieet, kunnen naar alle waarschijnlijkheid CNS voorkomen in algemeen gezonde populaties. Echter is bij HVZ patiënten verder onderzoek nodig naar het optimale voedingspatroon dat achteruitgang van de nierfunctie kan vertragen. Voor wat betreft de implementatie in voedingsadvies kan koffieconsumptie belangrijk zijn voor de preventie van CNS, met name bij patiënten met type 2 diabetes. Er is echter wel meer onderzoek nodig in voornamelijk Westerse cohorten van patiënten met type 2 diabetes, omdat het onderzoek hier beperkt is. Beperking van de consumptie van rood vlees kan ook belangrijk zijn voor het vertragen van de achteruitgang van de nierfunctie, zowel in de algemene populatie als bij HVZ patiënten. Wat betreft biomarkers in bloed zouden lage niveaus van plasma LA kunnen fungeren als indicator van versnelde achteruitgang van de nierfunctie bij HVZ patiënten. Serum urinezuur weerspiegelt waarschijnlijk meer gevorderde stadia van cardiometabole ziekten en kan in de klinische praktijk zorgen voor een nauwkeurigere risicobeoordeling. In sommige hoofdstukken vond ik veelbelovende resultaten voor de rol van voedingsfactoren bij het voorkomen van CNS in kwetsbare subgroepen met een hoger risico op CNS. Echter waren sommige van deze subgroepen erg klein (bijv. patiënten met diabetes, obesitas, CNS en vrouwen [alleen in het Alpha Omega Cohort]), en voorzichtigheid is daarom geboden bij het generaliseren van deze resultaten naar diabetes-, obesitas-, CNS patiënten en vrouwen.

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Lieve **papa**, lieve **mama**, jullie waren zo trots toen ik in 2019 ein-de-lijk een leuke baan had gevonden! Nu ben ik aan het eind en ik weet dat jullie nog altijd trots op mij zijn. Aangezien ik de eerste in de familie ben die dit traject heeft afgelegd, was het soms best een uitdaging om uit te leggen wat ik dan zoal elke dag doe. Hele dagen achter de computer werden thuis afgewisseld door fijne koffiemomentjes met **mama** en spelletjes met **Jasper**. **Jasper**, ondanks dat ik altijd verloor, had ik daarna wel nieuwe energie om verder te gaan met mijn werk. En toen ik op mezelf ging wonen, miste ik deze momentjes wel, hoor! Ik ben super trots en heb bewondering voor je, hoe je de afgelopen tijd in Boston en San Francisco twee Masters hebt gedaan. Je bent in positieve zin veranderd. Na 3000 keer solliciteren heb je nu dan toch een baan gevonden in Miami! Ik hoop je snel een keer op te kunnen zoeken daar. **Lieke**, ik ben ook heel trots op wat jij allemaal doet in Utrecht. Twee Bachelors tegelijkertijd, sporten, commissies en werk. En oh ja, dan vind je ook nog tijd om met je zus af en toe te eten en andere leuke dingen te doen. Bedankt hiervoor, dit was heel fijn als afleiding. **Sander**, hoe trots ben ik op jou dat jij nu ook je weg lijkt te hebben gevonden. Als een vis in het water ben jij door je opleiding heen gezwommen. En nu mag je aan het werk bij je stageplek. Jij houdt niet van spelletjes, maar zorgde wel op andere manieren voor afleiding. Dank hiervoor!

And last, but definitely not least, **Vincent**. Ik kan je niet genoeg bedanken. Eigenlijk verdien jij een hele pagina in dit dankwoord, want wat heb jij veel gedaan om mij door deze achtbaan heen te slepen! Het gebeurde regelmatig dat ik onverklaarbare errors kreeg in R en dat jij vanuit Verweggiestan de tijd vond om mij op afstand te helpen. Dan verzon je weer eens een geniaal for-loopje waardoor alles ineens wel klopte. Je probeerde mij uit te leggen hoe het for-loopje werkte, zodat ik het een volgende keer zelf zou kunnen. Helaas moest ik je dan een volgende keer toch weer bellen voor advies. In de laatste fase van dit proefschrift hielp je mij met formatten van alle hoofdstukken. Samen gingen we door tot in de late uurtjes en dat was een ware uitputtingsslag. Natuurlijk was jij er tussendoor ook als ik het mentaal even moeilijk had en je was er om de kleine overwinningen te vieren. We hebben prachtige reizen gemaakt en ik hoop dat wij nog heel veel andere mooie dingen mogen beleven. Bedankt, lieve schat, voor alles de afgelopen tijd. Op naar mooie nieuwe avonturen!

About the author

Curriculum vitae

List of publications

Overview of completed training activities

CURRICULUM VITAE

Anniek van Westing was born on 19 December 1993 in the hospital of Harderwijk. She completed secondary school at RSG 't Slingerbos in Harderwijk. After secondary school, she completed the Bachelor study program Biomedical Sciences at Utrecht University (2013-2016). In the final year of the Bachelor, she performed her thesis in which she compared the measurements of anti-Müllerian hormone assays using data of the Doetinchem Cohort Study. This thesis was then used as a basis for a publication in the peer reviewed journal Maturitas in 2017, and she was a co-author on this paper. Her interest in epidemiology was set back then. Therefore, she started the Master's program Epidemiology in 2016 at Utrecht University, in which she specialised in clinical epidemiology. During her Master's, she performed her thesis on the association between age at menopause and risk of stroke, using data of the European Prospective Investigation into Cancer and Nutrition (EPIC)-CVD case-cohort study. There, she learned about the R programming language and about the relatively new study design Mendelian randomisation. This thesis is currently accepted for publication in the Journal of the American Heart Association (JAHA).

In March 2019, Anniek joined the Nutrition and Disease chair group of the division of Human Nutrition and Health in Wageningen, as a PhD candidate. The scientific results of the PhD trajectory are described in this thesis. During her PhD trajectory, Anniek was co-author of seven other papers, including one from the Fatty Acids and Outcomes Research Consortium (FORCE). She was involved in teaching and (co)-supervised five BSc theses students and three MSc theses students. Anniek was also co-organiser of the bi-weekly chair group meetings of Nutrition and Disease during her entire PhD trajectory (2019-2023). She presented her work at various (inter)national conferences and attended various courses. In her free time, she likes to play tennis, read books and watch movies and series.

LIST OF PUBLICATIONS

Peer-reviewed publications

Van Westing AC, Cruijsen E, Voortman T, Geleijnse JM. Dairy products and kidney function decline after myocardial infarction: a prospective analysis in the Alpha Omega Cohort. *Clin Nutr.* 2023 Jun 3:S0261-5614(23)00166-8.

Amiri M, Raeisi-Dehkordi H, Verkaar AJCF, Wu Y, **van Westing AC**, Berk KA, Bramer WM, Aune D, Voortman T. Circulating lipoprotein (a) and all-cause and cause-specific mortality: a systematic review and dose-response meta-analysis. *Eur J Epidemiol.* 2023 May;38(5):485-499.

Van Westing AC, Ochoa-Rosales C, van der Burgh AC, Chaker L, Geleijnse JM, Hoorn EJ, Voortman T. Association of habitual coffee consumption and kidney function: a prospective analysis in the Rotterdam Study. *Clin Nutr*. 2023 Feb;42(2):83-92.

Ong KL, Marklund M,… **van Westing AC**, … and WU JH. Association of omega 3 polyunsaturated fatty acids with incident chronic kidney disease: pooled analysis of 19 cohorts. *BMJ*. 2023 Jan 18;380:e072909.

Amiri M, Karabegović I, **van Westing AC**, Verkaar AJCF, Beigrezaei S, Lara M, Bramer WM, Voortman T. Whole-diet interventions and cardiovascular risk factors in postmenopausal women: a systematic review of controlled clinical trials. *Maturitas.* 2022 Jan;155:40-53.

Van Westing AC, Eckl MR, Küpers LK, Pertiwi K, Hoogeveen EK, Geleijnse JM. Plasma fatty acids and kidney function decline in post-myocardial infarction patients of the Alpha Omega Cohort. *Nutr Metab Cardiovasc Dis*. 2021 May 6;31(5):1467-1476.

van Westing AC, Küpers LK, Geleijnse JM. Diet and kidney function: a literature review. *Curr Hypertens Rep.* 2020 Feb 3;22(2):14.

de Kat AC, Broekmans FJM, **van Westing AC**, Lentjes E, Verschuren WMM, van der Schouw YT. A quantitative comparison of anti-Müllerian hormone measurement and its shifting boundaries between two assays. *Maturitas.* 2017 Jul;101:12-16.

Expected publications

Van Westing AC, Heerkens L, Cruijsen E, Voortman T, Geleijnse JM. Association of diet quality with kidney function decline and the interaction with genetic risk in Dutch cardiovascular patients. *Submitted.*

Heerkens L#, **van Westing AC#**, Voortman T, Kardys I, Boersma E, Geleijnse JM. Serum uric acid is related to liver and kidney disease and 12-year mortality risk after myocardial infarction. *In revision.*

Cai Q, **van Westing AC**, Cao Y, Bakker SJL, Navis GJ, Geleijnse JM, de Borst MH. Coffee consumption and risk of kidney function decline in a Dutch population-based cohort. *Under review.*

Tschiderer L, Peters SAE, … **van Westing AC**, … and Onland-Moret NC. Age at menopause and the risk of stroke: Observational and Mendelian Randomization analysis in 204,244 postmenopausal women. *Accepted for publication in JAHA.*

Ong KL,… **van Westing AC**, … and Wu JH. Association of omega 6 polyunsaturated fatty acids with incident chronic kidney disease: pooled analysis of 19 cohorts. *In preparation.*

Laguzzi F, Åkesson A, **van Westing AC**,… and Leander K. Role of polyunsaturated fat in modifying cardiovascular risk associated with family history of cardiovascular disease. An Individual-Level Pooled Analysis of 15 observational studies. *In revision.*

Fretts M, … **van Westing AC**, … and Wu JH. Association of very long chain fatty acids with incident chronic kidney disease: pooled analysis of 19 cohorts. *In preparation.*

Published abstracts

Van Westing AC, Cruijsen E, Geleijnse JM. No beneficial associations between dairy products and kidney function after myocardial infarction. *Circulation.* 2021 May 18; 143:AP039

Van Westing AC, Eckl MR, Küpers LK, Pertiwi K, Hoogeveen EK, Geleijnse JM. Plasma fatty acids and kidney function decline: a prospective analysis of the alpha omega cohort. *Clin Nutr ESPEN.* 2020 Dec 1; 40, P490.

#Heerkens L and van Westing AC contributed equally to this work and share first authorship.

OVERVIEW OF COMPLETED TRAINING ACTIVITIES

Discipline specific activities

	Organiser and location	Year
WEON congress	Vereniging voor Epidemiologie (VvE), Groningen (NL)	2019
NuGOweek *"From Foodomics to Nutrigenomics: Translating food composition data into healthy diets"*	NuGO and Agroscope, Bern (CH)	2019
Dutch Nutritional Science Days	Nederlandse Academie van Voedingswetenschappen (NAV), Heeze (NL)	2019
Nutrition	ASN (online)	2020
Association Mapping: GWAS and Sequencing Data	University of Washington (online)	2020
42th European Congress on Clinical Nutrition & Metabolism	ESPEN (online)	2020
Mendelian Randomisation	University of Bristol (online)	2021
American Heart Association (AHA) EPI/Lifestyle Scientific Sessions	AHA (online)	2021
WEON congress	VvE (online)	2021
Dutch Nutritional Science Days	NAV (online)	2021
Advanced Epidemiological Methods	LUMC, Leiden (NL)	2021
WEON congress	VvE, Nijmegen (NL)	2022
Dutch Nutritional Science Days	NAV, Heeze (NL)	2022
Nefrologiedagen	Conference office Nefrologiedagen, Veldhoven (NL)	2023

General courses

	Organiser and location	Year
Pitch training	Human Nutrition and Health (HNH), Wageningen (NL)	2019
VLAG PhD week	VLAG, Baarlo (NL)	2019
Searching and Organising Literature	WUR Library, Wageningen (NL)	2019
PhD Workshop Carousel	WGS, Wageningen (NL)	2019
Project and Time Management	WGS, Wageningen (NL)	2020
Efficient Writing Strategies	Wageningen in'to languages (online)	2020
Scientific Writing	Wageningen in'to languages (online)	2021
Webinar & Workshop: how to present online	Wageningen in'to languages (online)	2021
Career Orientation	WGS, Wageningen (NL)	2022

Optionals

	Organiser and location	Year
Preparation of VLAG research proposal	VLAG, Wageningen (NL)	2019
MOOC Nutrition, Heart Disease and Diabetes	edX/WUR (online)	2019
MENU-D meetings	Nutrition and Disease, Wageningen (NL)	2019-2023
NAD paper club	Nutrition and Disease, Wageningen (NL)	2019-2023
Cardioclub	Nutrition and Disease, Wageningen (NL)	2019-2023
Rothman Lunches	Nutrition and Disease, Wageningen (NL)	2019-2023

Colophon

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