Clinical Nutrition 42 (2023) 1501–1509

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

Original article

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

Anniek C. van Westing [a, *], Esther Cruijsen [a], Trudy Voortman [a, b], Johanna M. Geleijnse [a]

[a] Division of Human Nutrition and Health, Wageningen University # Research, the Netherlands
[b] Department of Epidemiology, Erasmus MC, University Medical Center Rotterdam, the Netherlands

ARTICLE INFO

Article history:
Received 26 January 2023
Accepted 29 May 2023

Keywords:
Dairy
Milk
Kidney function
eGFR
Cohort study
CKD

SUMMARY

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 g/day for total milk, 20 g/day for hard cheeses, 18 g/day for plain yogurt, and 70 g/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 yogurt was adversely associated with annual $eGFR_{cr\text{-}cysC}$ change ($\beta_{total\ yogurt}$: −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 yogurt should be interpreted with caution. Our findings require confirmation in other cohorts of coronary heart disease patients.
© 2023 The Author(s). Published by Elsevier Ltd. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

1. 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 (i.e. calcium, potassium, magnesium), macronutrients (i.e. 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],

* Corresponding author. Stippeneng 4, 6708 WE Wageningen, the Netherlands.
E-mail address: anniek.vanwesting@wur.nl (A.C. van Westing).

https://doi.org/10.1016/j.clnu.2023.05.024
0261-5614/© 2023 The Author(s). Published by Elsevier Ltd. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

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 yogurt, however, was associated with a 4% lower risk of CVD mortality per increment of 25 g/day [19]. In the current study, we evaluated the association between habitual intake of milk, cheese, yogurt, and dairy desserts, and kidney function decline in post−MI patients of the Alpha Omega Cohort.

2. Materials & methods

2.1. 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).

2.2. 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, yogurt 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) yogurt, low-fat yogurt, 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].

2.3. 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 equation 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].

2.4. 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 categorized 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 categorized as no (0 g/day), low (>0−10 g/day), moderate (women: >10−20 g/day; men: >10−30 g/day), or high intake (women: >20 g/day; men: >30 g/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 Autoanalyzer (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].

2.5. 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 10th, 50th, and 90th percentile). The associations were visualized in graphs. Although figures were restricted to showing energy-adjusted intakes >0 to ≤400 g/day (total milk and low-fat milk), >0 to ≤80 g/day (cheese), and >0 to ≤200 g/day (total yogurt, low-fat yogurt, 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 yogurt, including low-fat yogurt (<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 1, we adjusted for age, sex, and total energy intake. In model 2, 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 3, 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 3. 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 3 for baseline $eGFR_{cr\text{-}cysC}$.

3. Results

3.1. 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).

3.2. 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. 1A), per 1-SD increment (Supplemental Fig. 3A), or across categories (Table 2). Similar results were obtained for low-fat milk (Table 2, Supplemental Fig. 2A, Supplemental Fig. 4A).

3.3. 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 g/day (Fig. 1B).

3.4. Yogurt intake and annual kidney function decline

Baseline median [IQR] energy-adjusted intake of yogurt 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 g/day) than in the lowest intake group (<10 g/day) (Table 2). This association remained in multivariable analyses of categories: patients with the highest intake (≥60 g/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 g/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 g/day (Fig. 1C). For low-fat yogurt, comparable results were obtained (Table 2, Supplemental Fig. 2B).

3.5. 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. 1D) 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. 3D).

3.6. 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

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

	Total population (n = 2169)	Energy-adjusted total milk consumption (grams/day)		
		<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)
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.
Abbreviations: 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; eGFRcr-cysC, estimated glomerular filtration rate based on creatinine and cystatin C; RAAS, renin-angiotensin-aldosterone system; CKD, chronic kidney disease.
[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 ≥8 h 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.

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			P_{trend}[a]
	Low	Intermediate	High	
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 yogurt	<10 (n = 931)	≥10–60 (n = 645)	≥60 (n = 593)	
Mean ± SD annual $eGFR_{cr\text{-}cysC}$ change, mL/min per 1.73m^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 yogurt	<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
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

Abbreviations: $eGFR_{cr\text{-}cysC}$, estimated glomerular filtration rate based on creatinine and cystatin C; SD, standard deviation.
[a] P_{trend} was assessed by treating the categorical variable as a continuous variable in the model.
[b] Model 1 included age, sex, and total energy intake.
[c] Model 2 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 3 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).

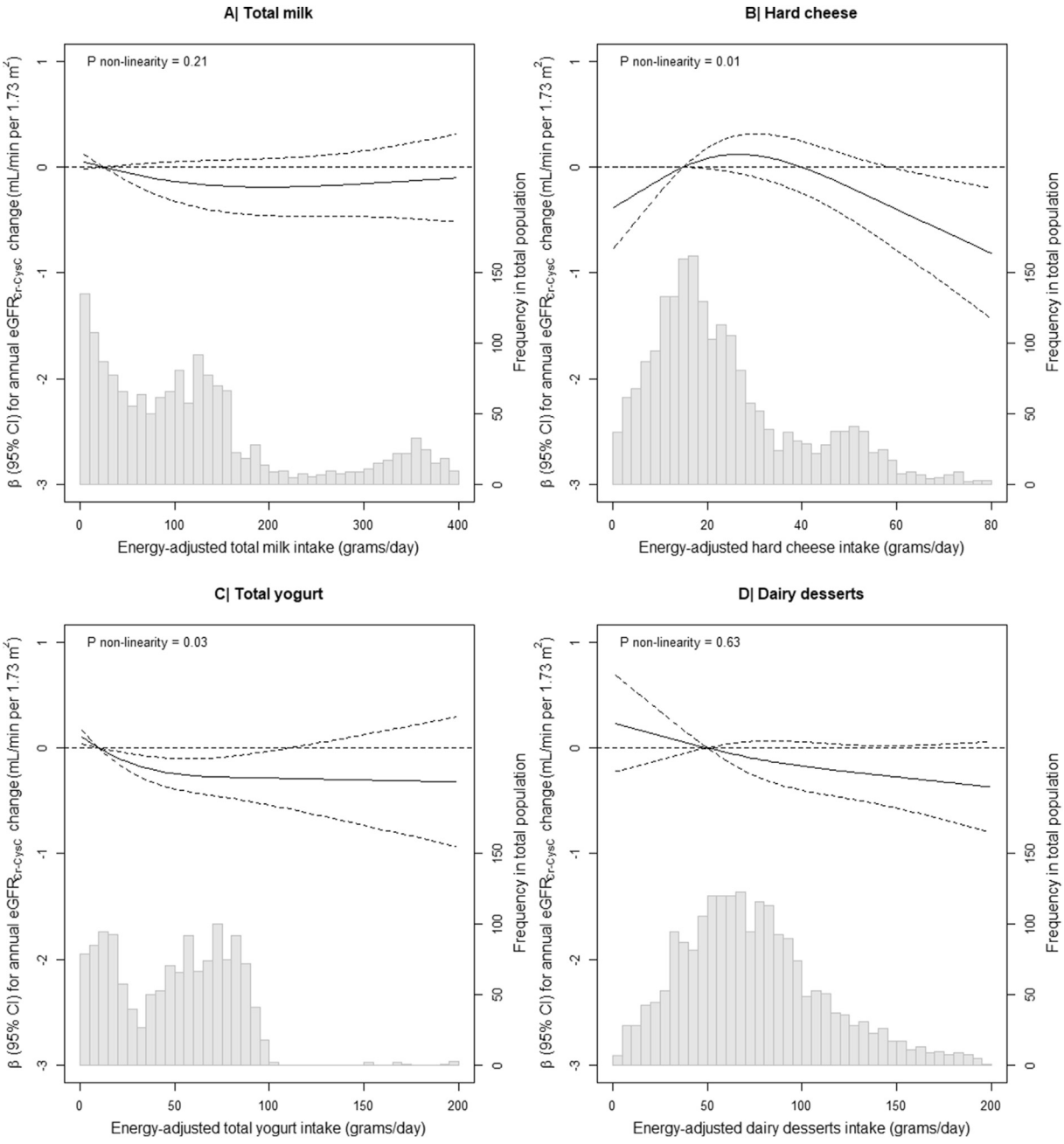

Fig. 1. Relationship between energy-adjusted intake of dairy products as continuous variable and annual $eGFR_{cr\text{-}cysC}$ change among 2,169 patients of the Alpha Omega Cohort. A| Total milk; B| Hard cheese; C| Total yogurt; D| Dairy desserts. Solid lines represent beta coefficients and dashed 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 (total milk), 15 grams/day (hard cheese), 10 grams/day (total yogurt), and 50 grams/day (dairy desserts) as reference points. 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. Abbreviations: $eGFR_{cr\text{-}cysC}$, estimated glomerular filtration rate based on creatinine and cystatin C; CIs, confidence intervals.

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 toward 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 Figs. 3 and 4). 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. 3D).

4. 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 yogurt are unclear, with RCS analysis showing more kidney function decline for

energy-adjusted intakes until ~40 g/day, and a flattened curve for higher intakes. The results for all dairy products were generally robust in all sensitivity and subgroup analyses.

4.1. 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, yogurt, coffee creamers, curd, pudding, porridge, custard, whipping cream) and annual eGFR decline, among 1488 participants with mildly decreased eGFR (mean ± SD eGFR 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.

4.2. Hard cheese and yogurt

In the present study, high versus 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 g/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]. Yogurt 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 hypothesize 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 yogurt 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 yogurt and diabetes risk [18], but yogurt was favourably associated with CVD mortality risk [19]. Therefore, our results for yogurt in relation to kidney function should be interpreted with caution and require further study.

4.3. 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.

4.4. 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 fiber (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.

4.5. 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, yogurt 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 24 h-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 yogurt, for which a beneficial association was found [19].

4.6. Conclusion

To conclude, our results suggest that dairy products may not delay kidney function decline after MI. Results for yogurt 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.

Funding statement

A.C. van Westing was supported by a grant from Jaap Schouten Foundation (grant no. JSF_SU_10_2018). T. Voortman reports grants from Erasmus MC, Erasmus University, Delft University, The European Society for Clinical Nutrition and Metabolism, National Dairy Association, and European Union. J.M. Geleijnse reports grants from the Ministry of Health, Welfare and Sports in the Netherlands, and the European Union. E. Cruijsen declares no conflict of interest. Data collection for the Alpha Omega Cohort was funded by the Dutch Heart Foundation (grant no. 200T401) and the National Institutes of Health (USA, NIH/NHLBI grant no. R01HL076200). Funding agencies had no role in the study design, data collection, analysis, decision to publish, or preparation of the manuscript.

Author contribution

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

Conflict of interest

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

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2023.05.024.

References

[1] van der Burgh AC, Rizopoulos D, Ikram MA, Hoorn EJ, Chaker L. Determinants of the evolution of kidney function with age. Kidney Int Rep 2021;6(12):3054–63.
[2] Eijkelkamp WB, de Graeff PA, van Veldhuisen DJ, van Dokkum RP, Gansevoort RT, de Jong PE, et al. Effect of first myocardial ischemic event on renal function. Am J Cardiol 2007;100(1):7–12.
[3] Esmeijer K, Geleijnse JM, de Fijter JW, Giltay EJ, Kromhout D, Hoogeveen EK. Cardiovascular risk factors accelerate kidney function decline in post-myocardial infarction patients: the Alpha omega cohort study. Kidney Int Rep 2018;3(4):879–88.
[4] Hoogeveen EK, Geleijnse JM, Giltay EJ, Soedamah-Muthu SS, de Goede J, Oude Griep LM, et al. Kidney function and specific mortality in 60-80 years old post-myocardial infarction patients: a 10-year follow-up study. PLoS One 2017;12(2):e0171868.
[5] van Westing AC, Kupers LK, Geleijnse JM. Diet and kidney function: a literature review. Curr Hypertens Rep 2020;22(2):14.
[6] Hu EA, Coresh J, Anderson CAM, Appel LJ, Grams ME, Crews DC, et al. Adherence to healthy dietary patterns and risk of CKD progression and all-cause mortality: findings from the CRIC (chronic renal insufficiency cohort) study. Am J Kidney Dis 2021;77(2):235–44.
[7] Sijtsma FP, Soedamah-Muthu SS, de Goede J, Oude Griep LM, Geleijnse JM, Giltay EJ, et al. Healthy eating and lower mortality risk in a large cohort of cardiac patients who received state-of-the-art drug treatment. Am J Clin Nutr 2015;102(6):1527–33.
[8] Eslami O, Shidfar F. Dairy products and chronic kidney disease: protective or harmful? a systematic review of prospective cohort studies. Nutrition 2018;55–56:21–8.
[9] Gaeini Z, Bahadoran Z, Mirmiran P, Feyzi Z, Azizi F. High-fat dairy products may decrease the risk of chronic kidney disease incidence: a long-term prospective cohort study. J Ren Nutr 2023;33(2):307–15.
[10] Wang H, Fox CS, Troy LM, McKeown NM, Jacques PF. Longitudinal association of dairy consumption with the changes in blood pressure and the risk of incident hypertension: the Framingham Heart Study. Br J Nutr 2015;114(11):1887–99.
[11] Aune D, Norat T, Romundstad P, Vatten LJ. Dairy products and the risk of type 2 diabetes: a systematic review and dose-response meta-analysis of cohort studies. Am J Clin Nutr 2013;98(4):1066–83.
[12] Ulven SM, Holven KB, Gil A, Rangel-Huerta OD. Milk and dairy product consumption and inflammatory biomarkers: an updated systematic review of randomized clinical trials. Adv Nutr 2019;10(suppl_2):S239–50.
[13] Rebholz CM, Tin A, Liu Y, Kuczmarski MF, Evans MK, Zonderman AB, et al. Dietary magnesium and kidney function decline: the healthy aging in neighborhoods of diversity across the life span study. Am J Nephrol 2016;44(5):381–7.
[14] Levin A, Stevens PE, Bilous RW, Coresh J, De Francisco AL, De Jong PE, et al. Kidney Disease: improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl 2013;3(1):1–150.
[15] Kalantar-Zadeh K, Fouque D. Nutritional management of chronic kidney disease. N Engl J Med 2017;377(18):1765–76.
[16] Mensink RP, World Health Organization. Effects of saturated fatty acids on serum lipids and lipoproteins: a systematic review and regression analysis. World Health Organization; 2016. https://apps.who.int/iris/handle/10665/246104.
[17] Brouwer IA, Wanders AJ, Katan MB. Effect of animal and industrial trans fatty acids on HDL and LDL cholesterol levels in humans–a quantitative review. PLoS One 2010;5(3):e9434.
[18] Jacobo Cejudo MG, Cruijsen E, Heuser C, Soedamah-Muthu SS, Voortman T, Geleijnse JM. Dairy consumption and 3-year risk of type 2 diabetes after myocardial infarction: a prospective analysis in the Alpha omega cohort. Nutrients 2021;13(9):3146.
[19] Cruijsen E, Jacobo Cejudo MG, Küpers LK, Busstra MC, Geleijnse JM. Dairy consumption and mortality after myocardial infarction: a prospective analysis in the Alpha Omega Cohort. Am J Clin Nutr 2021;114(1):59–69.
[20] Feunekes GI, Van Staveren WA, De Vries JH, Burema J, Hautvast JG. Relative and biomarker-based validity of a food-frequency questionnaire estimating intake of fats and cholesterol. Am J Clin Nutr 1993;58(4):489–96.
[21] Feunekes IJ, Van Staveren WA, Graveland F, De Vos J, Burema J. Reproducibility of a semiquantitative food frequency questionnaire to assess the intake of fats and cholesterol in The Netherlands. Int J Food Sci Nutr 1995;46(2):117–23.
[22] National Institute of Public Health and the Environment (RIVM). Nederlands voedingsstoffenbestand (NEVO) (Dutch food composition database). Available from: https://www.rivm.nl/en/dutch-food-composition-database/publications.
[23] Hoogeveen EK, Geleijnse JM, Kromhout D, Stijnen T, Gemen EF, Kusters R, et al. Effect of omega-3 fatty acids on kidney function after myocardial infarction: the Alpha Omega Trial. Clin J Am Soc Nephrol 2014;9(10):1676–83.
[24] Inker LA, Eneanya ND, Coresh J, Tighiouart H, Wang D, Sang Y, et al. New creatinine- and cystatin C-based equations to estimate GFR without race. N Engl J Med 2021;385(19):1737–49.
[25] Levey AS, Eckardt KU, Tsukamoto Y, Levin A, Coresh J, Rossert J, et al. Definition and classification of chronic kidney disease: a position statement from Kidney Disease: improving Global Outcomes (KDIGO). Kidney Int 2005;67(6):2089–100.
[26] Schuit AJ, Schouten EG, Westerterp KR, Saris WH. Validity of the Physical Activity Scale for the Elderly (PASE): according to energy expenditure assessed by the doubly labeled water method. J Clin Epidemiol 1997;50(5):541–6.
[27] Geleijnse JM, Giltay EJ, Schouten EG, de Goede J, Griep LMO, Teitsma-Jansen AM, et al. Effect of low doses of n-3 fatty acids on cardiovascular diseases in 4,837 post-myocardial infarction patients: design and baseline characteristics of the Alpha Omega Trial. Am Heart J 2010;159(4):539–546.e2.
[28] WHO Collaborating Centre for Drug Statistics Methodology. The Anatomical Therapeutic Chemical Classification (ATC) System. Oslo, Norway: WHO; 2009.
[29] Willett WC, Howe GR, Kushi LH. Adjustment for total energy intake in epidemiologic studies. Am J Clin Nutr 1997;65(4 Suppl):1220S–8S. discussion 9S-31S.
[30] Rodan AR. Potassium: friend or foe? Pediatr Nephrol 2017;32(7):1109–21.
[31] Ko GJ, Obi Y, Tortorici AR, Kalantar-Zadeh K. Dietary protein intake and chronic kidney disease. Curr Opin Clin Nutr Metab Care 2017;20(1):77–85.
[32] Park S, Lee S, Kim Y, Lee Y, Kang MW, Kim K, et al. Causal effects of relative fat, protein, and carbohydrate intake on chronic kidney disease: a Mendelian randomization study. Am J Clin Nutr 2021;113(4):1023–31.
[33] Herber-Gast GM, Biesbroek S, Verschuren WM, Stehouwer CD, Gansevoort RT, Bakker SJ, et al. Association of dietary protein and dairy intakes and change in renal function: results from the population-based longitudinal Doetinchem cohort study. Am J Clin Nutr 2016;104(6):1712–9.
[34] Malta D, Petersen KS, Johnson C, Trieu K, Rae S, Jefferson K, et al. High sodium intake increases blood pressure and risk of kidney disease. From the Science of Salt: a regularly updated systematic review of salt and health outcomes (August 2016 to March 2017). J Clin Hypertens (Greenwich) 2018;20(12):1654–65.
[35] Haring B, Selvin E, Liang M, Coresh J, Grams ME, Petruski-Ivleva N, et al. Dietary protein sources and risk for incident chronic kidney disease: results from the atherosclerosis risk in communities (ARIC) study. J Ren Nutr 2017;27(4):233–42.
[36] Gopinath B, Harris DC, Flood VM, Burlutsky G, Mitchell P. Associations between dairy food consumption and chronic kidney disease in older adults. Sci Rep 2016;6:39532.
[37] 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;31(5):1467–76.

[38] Pertiwi K, Küpers LK, Wanders AJ, de Goede J, Zock PL, Geleijnse JM. Associations of dairy and fiber intake with circulating odd-chain fatty acids in post-myocardial infarction patients. Nutr Metab (Lond). 2019;16:78.
[39] Esmeijer K, Geleijnse JM, de Fijter JW, Kromhout D, Hoogeveen EK. Dietary protein intake and kidney function decline after myocardial infarction: the Alpha Omega Cohort. Nephrol Dial Transplant 2020;35(1):106–15.
[40] Knight EL, Stampfer MJ, Hankinson SE, Spiegelman D, Curhan GC. The impact of protein intake on renal function decline in women with normal renal function or mild renal insufficiency. Ann Intern Med 2003;138(6):460–7.