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Plasma fatty acids and kidney function decline in post-myocardial infarction patients of the Alpha Omega Cohort

Anniek C. van Westing [a,*], Marion R. Eckl [a], Leanne K. Küpers [a], Kamalita Pertiwi [a], Ellen K. Hoogeveen [b], Johanna.M. Geleijnse [a]

[a] Division of Human Nutrition and Health, Wageningen University, Wageningen, the Netherlands
[b] Department of Nephrology, Leiden University Medical Center, Leiden, the Netherlands

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Omega-3 fatty acids

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 plasma fatty acids (FAs) as novel biomarkers of 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 diabetes (1.21, 0.24; 2.19) and in 402 patients with 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 diabetes.

The Alpha Omega Cohort is registered with clinicaltrials.gov, NCT03192410.

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], resulting in a strong increase in cardiovascular (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

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

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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]. Compared to patients with an 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]. Slowing down kidney function decline likely improves life expectancy. Therefore, there is a clinical need of novel biomarkers to identify post−MI patients with higher risk of accelerated kidney function decline.

Altered fatty acid (FA) profiles in blood have been observed in patients with CKD [11,12] and cardiometabolic disease [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 cardiometabolic disease 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 polyunsaturated fatty acids (PUFA) levels, assessed in total plasma [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]. However, hepatic FA metabolism may also affect plasma FAs, thereby, attenuating their correlation with diet as was observed for LA in cardiometabolic patients [29,30]. Interestingly, several population-based studies have shown an altered plasma FA composition in the presence of low-grade inflammation [31], insulin resistance [32,33], and excess abdominal fat [34].

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

Methods

Study design and population

We used data of 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 enrollment. Most patients received state-of-the-art medication, such as statins (86%) and antihypertensives (89%) [35]. 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 randomized trial of n-3 FAs versus placebo, which had no effect on recurrence of major cardiovascular events [35,36]. 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 [37]. 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 analyzed 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 °C by a high intraclass correlation coefficient for LA, EPA, and DHA (r > 0.90) [29].

Kidney function assessment

At baseline and after ∼40 months follow-up, serum creatinine (cr) and serum cystatin C (cysC) were measured in stored blood samples in a central laboratory [38,39]. Serum cysC was measured using a particle-enhanced immunonephelometric assay and serum cr was assessed

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using the modified kinetic Jaffé method as described in detail elsewhere [10]. We estimated GFR based on both serum cr and serum cysC using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation from 2012, which takes age, sex, and race into account [39]. 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 $\geq$3 ml/min per 1.73 m^2 [40].

Other measurements

Information about demographic variables and lifestyle habits was collected through self-administered questionnaires as previously described in detail elsewhere [35]. Smoking status was categorized into never, former, and current. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters; obesity was defined as BMI $\geq$ 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 [41,42]. Alcohol intake was assessed with the FFQ and categorized 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-min rest; and values were averaged. Hypertension was defined as high blood pressure (systolic blood pressure $\geq$140 mmHg or diastolic blood pressure $\geq$90 mmHg) or use of antihypertensive drugs. Blood lipids, such as total cholesterol, high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c), and triglycerides (mmol/L), and plasma glucose (mmol/L) were analysed using standardized kits (Hitachi 912, Roche Diagnostics, Basel, Switzerland). Diabetes mellitus was considered present in case of a self-reported physician's diagnosis, use of glucose lowering drugs, or elevated plasma glucose level ($\geq$7.0 mmol/L if fasted for $\geq$4 h or $\geq$11.1 mmol/L if not fasted).

CKD was defined as an eGFR <60 mL/min per 1.73 m^2 [4]. Medication was coded according to the Anatomical Therapeutic Chemical (ATC) Classification System [43]: antihypertensive drugs (CO2, C03, C07, C08, and C09), antithrombotic drugs (B01), and statins (C10AA and C10B) [35,36].

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-Q4). A threshold effect with an adverse association for Q1 (low plasma LA) vs Q2, Q3, and Q4 was observed. Therefore, Q2-Q4 were combined ("high") and compared to Q1 ("low"). For plasma EPA + DHA, C15:0, C17:0, and C14:0, the median of the distributions was used (below median as "low", above median as "high"). Regression coefficients are presented as unstandardized betas with 95% confidence intervals (CIs). For each FA, 2 models were created. Model 1 included age, sex, and total serum cholesterol. Model 2 additionally included BMI, smoking status (3 categories), alcohol intake (4 categories), hypertension (2 categories), hours of fasting before blood collection, statin use (2 categories), and all remaining plasma FAs under study (either LA, EPA + DHA, C15:0, C17:0, C14:0, depending on the exposure). P values for trend were calculated across the four categories of plasma LA. Supplemental intake of low doses of n-3 FAs during the Alpha Omega Trial [36] 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 [44].

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 [45], 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 = 1165 vs n = 1164, respectively) when analysing plasma EPA + DHA. Finally, analyses for plasma LA were repeated in subgroups of statin use (n = 1985 statin users and n = 344 non-statin users), because statins may influence plasma LA levels [29]. For each of the subgroup analyses, potential effect modification was tested by including interaction terms with each plasma FA under study in model 2. RStudio version 3.6.0 was used for all analyses and a two-sided p-value <0.05 was considered statistically significant.

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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/1.73 m^2, corresponding to a yearly decline of 1.38 ± 3.79 mL/min per 1.73 m^2 (Supplemental Fig. 2).

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). These associations were roughly similar, when analysing plasma LA in quartiles (Supplemental Table 1). 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 diabetes (1.21 (0.24; 2.19) ml/min per 1.73 m^2) or 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). The results for plasma LA did not differ by statin use (Supplemental Table 2, P interaction = 0.75).

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

Table 1 Baseline characteristics of 2329 post–MI patients of the Alpha Omega Cohort by availability of cholesteryl esters.

	Cholesteryl esters (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 1.73m^2	78.5 ± 18.7
CKD, n (%)[j]	402 (17.3)
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)
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. Abbreviations: MI, myocardial infarction; BMI, body mass

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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, monounsaturated fatty acids; PUFA, poly-unsaturated fatty acids; ALA, alpha-linolenic acid; AA, arachidonic acid; LA, linoleic acid; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid.

[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] Categorized 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.

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 3). 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 3), which was also confirmed by the continuous analyses (Supplemental Table 3). Analyses in strata of diabetes, in those without CKD, or with lower and higher plasma LA levels, yielded similar results (Fig. 2, Supplemental Table 3). 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 CKD (Supplemental Table 3). However, no indication of effect modification by diabetes (P interaction = 0.46) and plasma LA (P interaction = 0.86) was found.

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% from 2329 patients), and values for C17:0 were zero or below the detection limit for 747 patients (32% from 2329 patients). For both plasma OCFAs, a stronger mean annual eGFR decline in the patient group with higher plasma OCFAs was observed (Supplemental Tables 4 and 5). 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 4). This was confirmed by analyses on a continuous scale (Supplemental Table 4). Results were not altered after exclusion of patients with diabetes or CKD (Fig. 3, Supplemental Table 4). No association was found for patients with diabetes or CKD (Supplemental Table 4). For plasma C17:0, similar results for all patients and for those without diabetes or CKD were observed (Fig. 3, Supplemental Table 5). In patients with diabetes or CKD, no association was shown between plasma C17:0 and eGFR change (Supplemental Table 5). 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 6). 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 6), which was confirmed by analyses on a continuous scale (Supplemental Table 6). Results were similar in strata of diabetes and in non-CKD patients (Fig. 3, Supplemental Table 6). No association was found for patients with CKD (Supplemental Table 6). Effect modification by diabetes (P interaction = 0.57) or CKD (P interaction = 0.31) was not present.

Discussion

This study showed that patients with higher plasma LA levels, the most abundant FA in plasma CE, had 40% less kidney function decline per year after MI. This association was more pronounced in patients with 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 [39]. 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

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Table 2 Betas and 95% CI for high vs low plasma LA in CE and per SD and annual eGFR change (ml/min per 1.73 m^2) in 2329 post−MI patients of the Alpha Omega Cohort, overall and in subgroups of diabetes, CKD, and plasma EPA + DHA.

	Plasma LA (% total FAs)		P value	Per SD[b]	P value
	Low[a]	High[a]			
All patients (n = 2329)					
Cut off values	≤46.9	>46.9			
Median (IQR)	44.4 (42.5; 45.8)	51.9 (49.4; 54.7)			
Mean ± SD annual eGFR change	−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 (n = 437)[e]					
Median (IQR)	43.8 (41.9; 44.8)	51.4 (49.1; 54.3)			
Mean ± SD annual eGFR change	−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 (n = 1892)					
Median (IQR)	44.5 (42.7; 46.0)	51.9 (49.5; 54.7)			
Mean ± SD annual eGFR change	−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 (n = 402)[f]					
Median (IQR)	44.3 (42.4; 45.9)	52.6 (49.5; 55.5)			
Mean ± SD annual eGFR change	−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 (n = 1927)					
Median (IQR)	44.4 (42.5; 45.8)	51.8 (49.4; 54.5)			
Mean ± SD annual eGFR change	−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
Low plasma EPA + DHA patients (n = 1163)[g]					
Median (IQR)	46.0 (44.1; 47.4)	53.3 (51.1; 55.7)			
Mean ± SD annual eGFR change	−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]	Ref	0.40 (−0.15; 0.96)	0.15	0.17 (−0.10; 0.44)	0.21
High plasma EPA + DHA patients (n = 1166)[g]					
Median (IQR)	43.2 (41.6; 44.5)	50.1 (47.8; 52.8)			
Mean ± SD annual eGFR change	−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]	Ref	0.23 (−0.29; 0.75)	0.39	0.16 (−0.09; 0.42)	0.21

CI, confidence interval; LA, linoleic acid; CE, cholesteryl esters; SD, standard deviation; eGFR, estimated glomerular filtration rate; MI, myocardial infarction; CKD, chronic kidney disease; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; FAs, fatty acids; IQR, interquartile range.

[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), and 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 (except when used as stratifying variable).

[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.

proteinuria. Furthermore, patients who died during follow-up (n = 233, Supplemental Fig. 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 probably less healthy. Lastly, patients included in our analysis only had measurements of FAs in CE, while other studies make use of phospholipids (PL) or total plasma [14,18]. In a sub-study of the Alpha Omega Cohort, we measured FAs in multiple lipid compartments, showing high correlations (r > 0.80) for EPA and DHA when comparing CE, PL and total plasma [29]. Therefore, we consider it unlikely that the choice of CE explains the lack of an association of EPA and DHA with kidney function in our cohort of post−MI patients.

Data on plasma LA and kidney function are scarce, particularly in large patient cohorts. The InCHIANTI study

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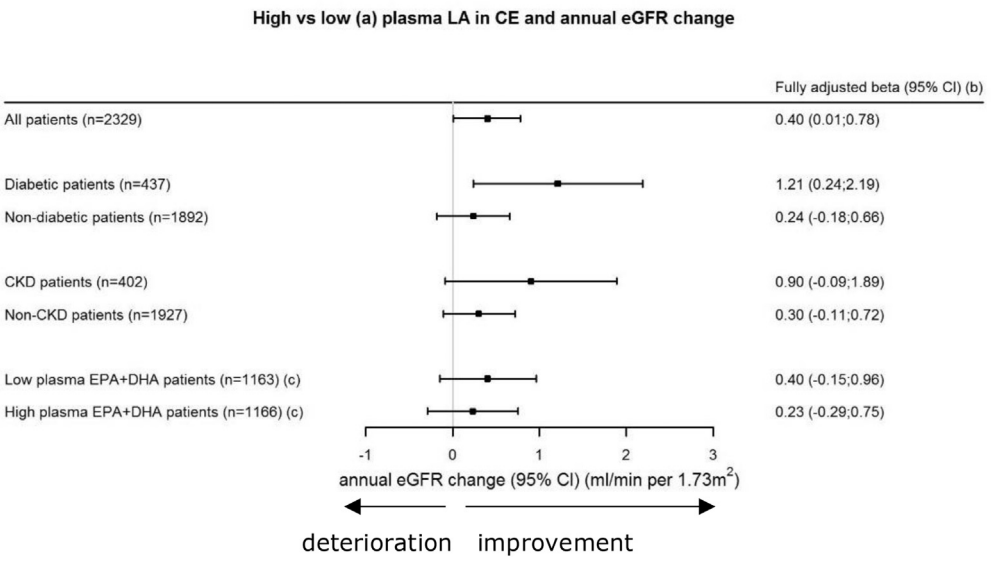

Figure 1 Forest plot high (Q2-Q4) vs low (Q1) plasma LA in CE and annual eGFR change. (a). $Low_{all\ patients}$: ≤46.9%, $high_{all\ patients}$: >46.9%; $low_{diabetic\ patients}$: ≤46.1%, $high_{diabetic\ patients}$: >46.1%; $low_{non\text{-}diabetic\ patients}$: ≤ 46.6%, $high_{non\text{-}diabetic\ patients}$: >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 (except when used as stratifying variable); (c). Low and high plasma EPA + DHA defined using the median of the distribution (1.72% total FAs in CE); LA, linoleic acid; CE, cholesteryl esters; eGFR, estimated glomerular filtration rate, CI, confidence interval; CKD, chronic kidney disease; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid.

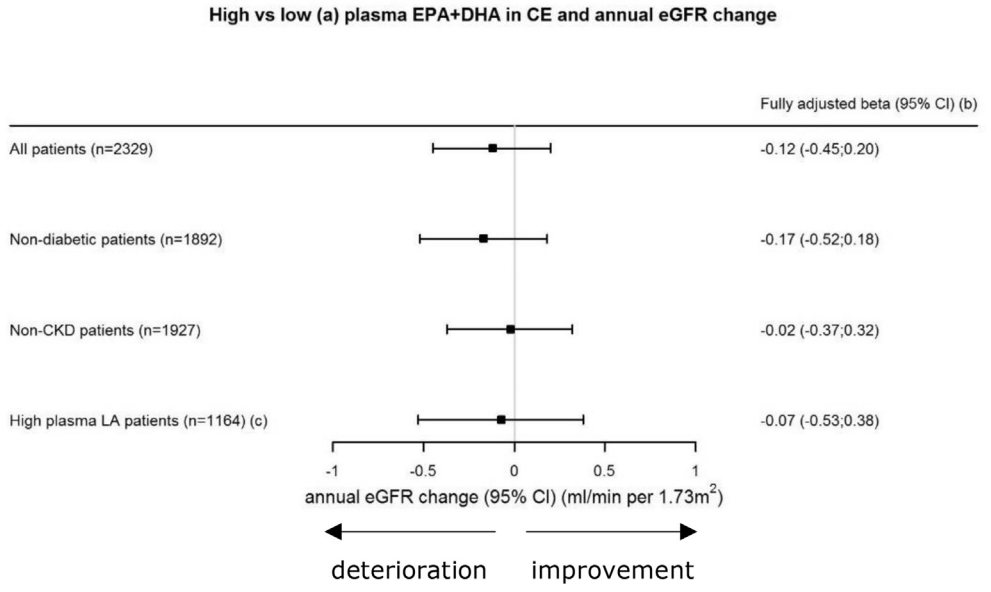

Figure 2 Forest plot high (above median) vs low (below median) plasma EPA + DHA in CE and annual eGFR change. (a). $Low_{all\ patients}$: ≤1.72%, $high_{all\ patients}$: >1.72%; $Low_{non\text{-}diabetic\ patients}$: ≤1.71%, $high_{non\text{-}diabetic\ patients}$: >1.71%; $Low_{non\text{-}CKD\ patients}$: ≤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 (except when used as stratifying variable); (c). High plasma LA defined using the median of the distribution (50.1% total FAs in CE); EPA, eicosapentaenoic acid, DHA, docosahexaenoic acid; CE, cholesteryl esters; eGFR, estimated glomerular filtration rate; CI, confidence interval; CKD, chronic kidney disease; LA, linoleic acid.

in 676 generally healthy Italian elderly showed less kidney function decline over three years of follow-up for higher plasma LA, assessed in total plasma [25]. Yet, inverse associations between plasma LA measured in various lipid compartments and other cardiometabolic diseases, such as CVD and obesity, have been reported in pooled analyses of

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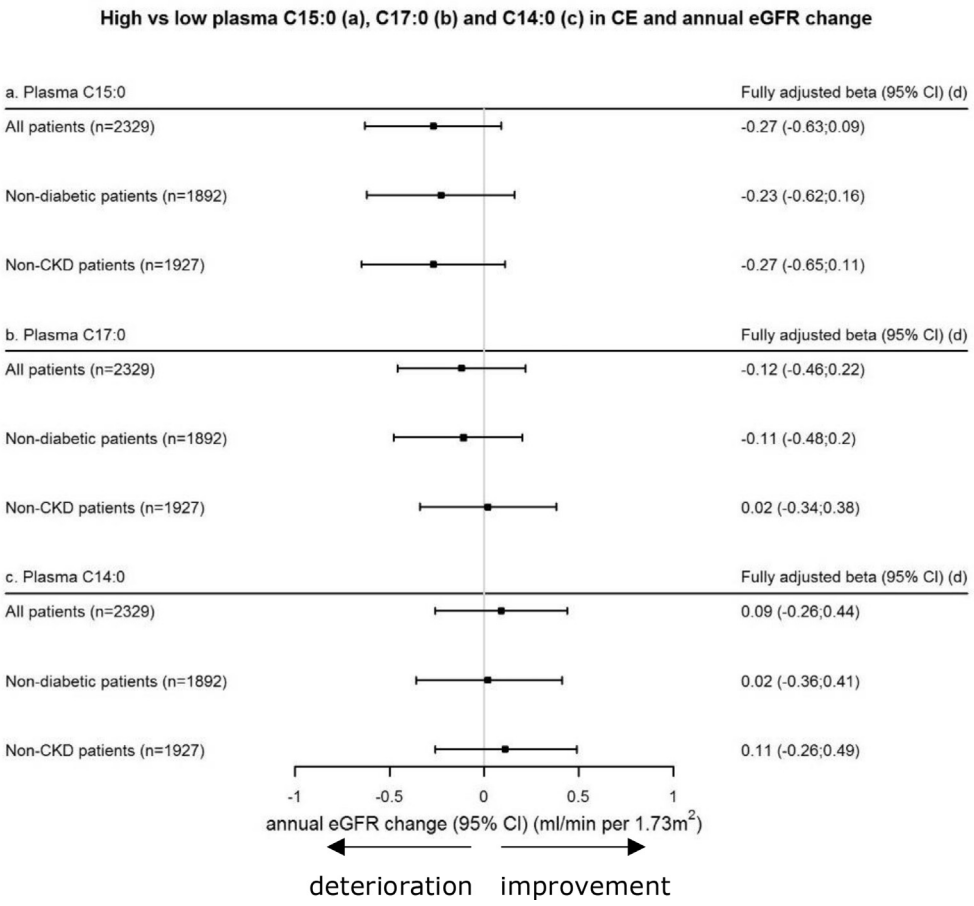

Figure 3 Forest plot high (above median) vs low (below median) plasma C15:0, C17:0 and C14:0 in CE and annual eGFR change. (a). $Low_{all,\ non\text{-}diabetic,\ non\text{-}CKD\ patients}$: ≤0.16%, $high_{all,\ non\text{-}diabetic,\ non\text{-}CKD\ patients}$: >0.16%; all patients group includes 2.8% with non-detectable or true zero; non-diabetic patients group includes 2.5% with non-detectable or true zero; non-CKD patientsgroup 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.

population-based studies [46,47]. In a previous analysis of the Alpha Omega Cohort, lower plasma LA levels in CE were related to a higher diabetes risk, for which we hypothesized that dysregulation of hepatic FA metabolism could play a role [30]. Now, in the same cohort, we found low plasma LA to be a predictor of kidney function decline, especially in patients with diabetes or CKD. Also here, impaired liver function may be involved, supported by accumulating evidence for a link between non-alcoholic fatty liver disease and CKD [48]. Findings from the present analysis cannot merely be translated to LA intake from the diet, since plasma and dietary LA were poorly correlated in our cohort of post−MI patients (r = 0.15) [29].

Plasma EPA + DHA, an accepted biomarker of fatty fish intake [26], was not associated with kidney function decline in our cohort of post−MI patients. This is in contrast with a previous intervention study in the same patients, showing 30% less kidney function decline after ~40 months of EPA + DHA supplementation (400 mg/day) on top of habitual daily intake [40]. Beneficial and significant associations for n-3 PUFAs (α-linolenic acid (ALA), EPA and DHA) in total plasma were found in the previously described InCHIANTI study [25]. The Italian cohort consumed a Mediterranean-type of diet with relatively high amounts of fish, while our Dutch post−MI patients had a median fish intake of only 12 g/day. Possibly, higher intakes of EPA and DHA or fish are needed to exert a beneficial effect on kidney function.

Dairy intake, particularly low-fat dairy, has been associated with a better kidney function, possibly due to blood pressure lowering minerals such as calcium, potassium and magnesium [49,50]. Plasma OCFAs have been identified as biomarkers of dairy intake, also in the present cohort [51], but we found no association of OCFAs with kidney function decline. Plasma C14:0 has also been proposed as a dairy biomarker [52], although it may also reflect saturated fat intake from coconut or palm oil [53].

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We found no associations between plasma C14:0 and eGFR change, in line with findings from population-based studies on other cardiometabolic endpoints [22,24,54].

In conclusion, higher plasma LA predicted less kidney function decline after MI, especially in patients with diabetes or CKD. Substantial differences in decline were observed, which could have major implications for risk of CKD and premature mortality [10]. The clinical relevance of plasma LA in CHD patients in relation to kidney function and other cardiometabolic health outcomes warrants confirmation in other prospective cohort studies.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.numecd.2021.01.012.

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