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Risk factors of chronic kidney disease progression: Dutch cohort studies

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Citation
Esmeijer, K. (2020, March 19). *Risk factors of chronic kidney disease progression: Dutch cohort studies*. Retrieved from https://hdl.handle.net/1887/137184

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Author: Esmeijer, K.
Title: Risk factors of chronic kidney disease progression: Dutch cohort studies
Issue Date: 2020-03-19

Chapter 2 –

Cardiovascular risk factors accelerate kidney function decline in post-myocardial infarction patients: The Alpha Omega Cohort study

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Kidney Int Rep. 2018, 3: 879-888

ABSTRACT

Background: Impaired kidney function is a robust risk factor for cardiovascular mortality. The age-related annual kidney function decline after age 40y of 1.0 mL/min/1.73m^2, is doubled in post-myocardial infarction (MI) patients. We investigated the impact of the number of cardiovascular risk factors (including unhealthy lifestyle) on annual kidney function decline, in 2426 post-MI patients (60-80y) of the prospective Alpha Omega Cohort study.

Methods: Glomerular filtration rate was estimated by serum cystatin C ($eGFR_{cysC}$) and combined creatinine-cystatin C ($eGFR_{cr-cysC}$), using the CKD-EPI equations. Data were analysed by multivariable linear and logistic regression.

Results: At baseline, mean (SD) $eGFR_{cysC}$ and $eGFR_{cr-cysC}$ were 81.5 (19.6) and 78.5 (18.7) mL/min/1.73m^2, respectively. Of all patients, 79% were men, 19% had diabetes, 56% had high blood pressure (≥140/90 mmHg), 16% were current smokers, 56% had high serum low-density lipoprotein (LDL ≥2.5 mmol/L), and 23% were obese (body-mass index ≥30.0 kg/m^2). After multivariable adjustment, the additional annual $eGFR_{cysC}$ decline (95%-CI) was in patients with *vs* without diabetes -0.90 (-1.23; -0.57) mL/min/1.73m^2, in patients with high *vs* normal blood pressure -0.50 (-0.76; -0.24), in obese *vs* non-obese patients -0.31 (-0.61; 0.01), and in current compared to non-smokers -0.19 (-0.54; 0.16) mL/min/1.73m^2. High LDL was not associated with accelerated $eGFR_{cysC}$ decline. Similar results were obtained with $eGFR_{cr-cysC}$.

Conclusions: In older stable post-MI patients without cardiovascular risk factors, the annual kidney function decline was -0.90 (-1.16; -0.65) mL/min/1.73m^2. In contrast, in post-MI patients with ≥3 cardiovascular risk factors, the annual kidney function decline was 2.5-fold faster: -2.37 (-2.85; -1.89) mL/min/1.73m^2.

INTRODUCTION

The incidence of chronic kidney disease (CKD) shows an increasing trend worldwide.[1] Impaired kidney function is a robust and independent risk factor for cardiovascular and all-cause morbidity and mortality.[2] In industrialized countries, in healthy individuals after age 40y, kidney function gradually declines annually about 0.8 to 1.0 mL/min/1.73m^2.[3, 4] In contrast, post-myocardial infarction (MI) patients have an accelerated kidney function decline of about 2.2 mL/min/1.73m^2 per year, and are thus more prone to develop CKD.[5]

Classic modifiable cardiovascular risk factors such as hypertension and diabetes are important drivers for the development of CKD.[6-10] The association between elevated low-density lipoprotein (LDL) levels and kidney function decline is less clear.[11] Lifestyle factors, such as smoking of cigarettes and adiposity, may increase the risk of hypertension and diabetes. All previous mentioned cardiovascular risk factors can have an unfavourable effect on kidney function owing to increased inflammation, oxidative stress, endothelial dysfunction, and disturbed coagulation. For example, accumulation of visceral adipose tissue may lead to increased production of inflammatory mediators by adipocytes, which may contribute to glomerular and interstitial fibrosis.[12, 13]

Survival after MI has been improving, as a result of improved health care and pharmaceutical treatment. These trends, together with the global tendency towards a less healthy lifestyle and population aging, have resulted in a considerable pool of patients at high risk for CKD.[14] Little is known about the beneficial effect of optimal treatment of cardiovascular risk factors and healthy life style on kidney function decline in post-MI patients. Since adequate drug-treatment of cardiovascular risk factors and modest lifestyle alterations are achievable and may retard kidney function decline in post-MI patients, we studied the association of modifiable cardiovascular risk factors (including lifestyle) in older stable post-MI patients of the Alpha Omega Cohort.

METHODS

Participants

This is a secondary analysis of the prospective Alpha Omega Cohort study (ClinicalTrials.gov no. NCT03192410). We included patients from the Alpha Omega Trial, a randomized controlled multi-center trial of omega-3 (n-3) fatty acids supplementation in 4837 patients with a verified history of MI. Patients were aged 60-80 years, and were receiving state-of-the-art antihypertensive, antithrombotic and lipid-modifying drug treatment, according to the international guidelines, as described elsewhere.[15, 16] The trial started in 2002 and ended in 2009. Patients with severe heart failure (NYHA stage IV) were excluded. For the present observational study, patients were selected from whom non-fasting blood was drawn at baseline and after 41 months. Owing to financial constraints two blood samples were available only for 2426 patients (50% of the cohort, i.e. those randomized before August 2005). Of all patients randomized prior to August 2005 (n=2918), 233 patients deceased during follow-up, and 259 patients had missing blood samples or refused participation (Supplementary Figure S1). This study was conducted in accordance with the Helsinki Declaration and was approved by a central medical ethics committee in the Netherlands. Written informed consent was obtained from all patients. Design and reporting of the current study was performed in accordance with the STROBE Statement for cohort studies.[17]

Data collection

Patients were interviewed and physically examined by trained research nurses at baseline and after 41 months. Standardized blood handling procedures for the Alpha Omega Trial are described in detail elsewhere.[18, 19] Lipid, glucose and high-sensitivity C-reactive protein (hsCRP) levels were determined as described elsewhere.[20] Information on demographic variables, lifestyle habits, current health status, and medical history were collected by self-administered questionnaires as previously described in detail.[18] Questionnaires were checked by research nurses. Information on smoking of cigarettes was obtained by self-reported questionnaires, and was dichotomized into current smoking *vs* non-smoking (former or never smoking). Alcohol consumption was dichotomized into at least 1 glass/week *vs* less than 1 glass/week. Systolic and diastolic blood pressure (1st and 5th Korotkoff sound, respectively) were measured at the left upper arm with the patient seated, after a 10 min. seated rest, using an automatic device (Omron HEM-711, Omron Healthcare Europe B.V., Hoofddorp, The Netherlands). The average of two blood pressure measurements was taken. High blood pressure was defined as inadequately controlled blood pressure

according to the latest recommendations of the international guideline of the European Society of Cardiology: systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg.[21] Diabetes mellitus was considered present in case of a self-reported physician diagnosis, use of glucose-lowering drugs, and/or hyperglycemia. Hyperglycemia was defined as serum glucose ≥7.0 mmol/L for patients who had fasted 4 hours or ≥11.1 mmol/L for non-fasting patients. Serum LDL was calculated using the Friedewald formula.[22] High LDL was defined as serum level ≥2.5 mmol/L.[23] Body-mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Obesity was defined as a BMI of ≥30.0 kg/m^2, according to World Health Organization guidelines.[24] Medication was coded according to the Anatomical Therapeutic Chemical (ATC) Classification System.

Kidney function assessment

At baseline and 41 months follow-up, serum cystatin C (cysC) was measured from stored blood samples in a central laboratory. We used calibrators and assays of the same lot code, which was stable (no downward drift).[25] Serum creatinine (cr) was measured by the modified kinetic Jaffé method, as previously described in detail.[25] We estimated glomerular filtration rate based on cystatin C ($eGFR_{cysC}$) and combined creatinine-cystatin C ($eGFR_{cr-cysC}$) at baseline and after 41 months, using the CKD-EPI equations from 2012, taking into account age, sex and race.[26] Both $eGFR_{cysC}$ and $eGFR_{cr-cysC}$ are regarded superior measures of kidney function compared to eGFR based on creatinine alone. In the main analyses we use $eGFR_{cysC}$ as outcome, results for $eGFR_{cr-cysC}$ as outcome are reported in the supplements. From each individual, eGFR decline was calculated by subtracting the eGFR at baseline from the eGFR after 41 months. Assuming a linear decline over time, we then estimated the annual kidney function decline. Rapid kidney function decline was defined as an annual decline of >3 mL/min/1.73m^2.[27, 28]

Data analysis

Baseline characteristics are presented for all patients and according to the number of cardiovascular risk factors. Baseline data are presented as mean (SD), median (interquartile range), or number (percentage) when appropriate. The following data were missing: LDL cholesterol (n=116), BMI (n=4), level of education (n=4), blood pressure (n=3), alcohol consumption (n=3). We accounted for missing data by multiple imputation, using five imputations, and including all relevant baseline variables and the outcome in the model.

We used analysis of covariance (ANCOVA) to compare annual $eGFR_{cysC}$ decline rates for presence *vs* absence of a priori selected cardiovascular risk factors (including unhealthy lifestyle): diabetes, high blood pressure, high LDL levels,

current cigarette smoking, and obesity. In addition, we used multivariable logistic regression to estimate for each cardiovascular risk factor the risk of rapid kidney function decline. In all analyses, we used patients without the cardiovascular risk factor as the reference. All analyses are presented crude and adjusted for potential confounders: age, sex and three dummy variables for the four n-3-fatty acid treatment groups of the Alpha Omega Trial (model 1). In model 2 we adjusted in addition to model 1, for alcohol use (less than *vs* at least one glass/week), level of education (three dummy variables), and the five a priori selected cardiovascular risk factors.. Analyses for obesity were not adjusted for diabetes, high blood pressure and high LDL, because these factors are in the causal pathway between obesity and kidney function decline. Analyses were not adjusted for baseline eGFR, because baseline-adjustment in models with change-scores as dependent variable results in biased and inflated estimates.[29] We explored the presence of effect modification between age or sex and the modifiable risk factors with regard to kidney function decline by including interaction terms in our linear regression models. Furthermore, we repeated analyses in strata of baseline eGFR (eGFR <60, 60<90, ≥90 mL/min/1.73m^2).

Finally, we calculated the rate of kidney function decline and risk of rapid kidney function decline according to the number of cardiovascular risk factors present in each patient. In these analyses we included diabetes, high blood pressure, current smoking, and obesity. High LDL was excluded because of lack of evidence that modifying LDL level affects cardiovascular risk.[30] Patients without cardiovascular risk factors have by definition an optimal cardiovascular risk profile and a healthy lifestyle, e.g. are considered being optimally treated for the included risk factors according to the latest guidelines of the European Society of Cardiology: blood pressure <140/90 mmHg, no diabetes, never smoked cigarettes or ceased smoking, and no obesity (BMI<30 kg/m^2).[31] A linear trend was evaluated by including a variable representing number of cardiovascular risk factors into the linear regression model.

Sensitivity analyses

We repeated all analyses without multiple imputation, using a complete case analysis. Next, we repeated the analyses adjusting for continuous instead of dichotomized variables, e.g. for BMI instead of obesity, and for systolic blood pressure instead of high blood pressure. Main analyses were repeated after adjustment for time since MI, hsCRP levels or use of RAS blocking drugs. We repeated the analyses in patients persistently (at baseline and after 41 months of follow-up) using RAS blocking drugs. Finally, we repeated the main analyses using $eGFR_{cr-cysC}$ as outcome. In these analyses we excluded 82 patients of whom serum creatinine was not available due to technical failure or analytical

disturbance.[25] We considered two-sided P-values <0.05 statistically significant. All analyses were performed using SPSS 23.0 (SPSS, Inc., Chicago, IL).

RESULTS

Baseline characteristics

Baseline characteristics of all patients (n=2426), and stratified for the number of cardiovascular and lifestyle risk factors, are presented in Table 1. The mean (SD) age of the total study cohort was 68.9 (5.4) years, 79.4% were men, median time since MI was 4.0 years, mean (SD) $eGFR_{cysC}$ and $eGFR_{cr-cysC}$ were 81.5 (19.6) and 78.5 (18.7) mL/min/1.73m^2, respectively. Of all patients, 23% were obese, 16% were current smokers, 67% were former smokers, 44% had a blood pressure within the target range, 87% used anti-hypertensive medication, 54% used RAS blocking drugs of whom 92% persisted on RAS blocking drugs, and 19% had diabetes of whom 71% used glucose lowering medication. Finally, 44% of patients had normal LDL, 85% used statins, of whom 95% persisted on statins. Of all patients with high LDL (n=990) at baseline, 10% started with a statin during follow-up.

Table 1: Baseline characteristics of 2426 post-MI patients of the Alpha Omega Cohort according to the number of cardiovascular risk factors (obesity, high blood pressure, diabetes, current smoking).

		Number of cardiovascular risk factors			
	All patients n=2426	0 n=598	1 n=1088	2 n=573	≥3 n=167
Age, y	68.9 ± 5.4	68.3 ± 5.3	69.6 ± 5.4	68.5 ±5.5	68.9 ± 5.4
Men, no. (%)	1927 (79.4)	497 (83.1)	878 (80.7)	430 (75.0)	122 (73.1)
Race, white, no. (%)	2398 (98.8)	589 (98.5)	1078 (99.1)	567 (99.0)	164 (98.2)
Time since MI, y	4.0 (2.0–6.4)	3.3 (1.6–5.9)	4.0 (1.9–6.5)	4.4 (2.4–6.6)	4.8 (3.1–7.4)
Educational level, no. (%)					
Only elementary/low	1374 (57.0)	319 (53.6)	603 (55.7)	353 (62.0)	99 (59.6)
Moderate	738 (30.6)	190 (31.9)	344 (31.8)	152 (26.7)	52 (31.3)
High[a]	300 (12.4)	86 (14.5)	135 (12.5)	64 (11.2)	15 (9.0)
Current smoking, no. (%)	386 (15.9)	0	100 (9.2)	196 (34.2)	90 (53.9)
Alcohol consumption,[b] no. (%)	1759 (72.5)	450 (75.3)	813 (74.7)	390 (68.1)	106 (63.5)
Obese,[c] no. (%)	554 (22.8)	0	146 (13.4)	268 (46.8)	140 (83.8)
Body-mass index, kg/m^2	27.7 ± 3.6	26.0 ± 2.3	27.1 ± 3.1	29.3 ± 4.1	32.1 ± 3.5
High blood pressure,[d] no. (%)	1064 (43.9)	0	744 (68.4)	457 (79.8)	161 (96.4)
Systolic blood pressure, mmHg	143.3 ± 21.4	125.1 ± 10.3	147.6 ± 21.6	150.8 ± 19.6	154.8 ± 17.7
Diastolic blood pressure, mmHg	81.4 ± 10.8	75.1 ± 7.8	83.1 ± 10.9	83.2 ± 10.8	86.3 ± 9.4
Anti-hypertensive drugs,[e] no. (%)	2111 (87.0)	502 (83.9)	954 (87.7)	507 (88.5)	148 (88.6)
ACE inhibitors/ATII blockers	1309 (54.0)	311 (52.0)	576 (52.9)	327 (57.1)	95 (56.9)
Beta blockers	1585 (65.3)	371 (62.0)	718 (66.0)	385 (67.2)	111 (66.5)
Calcium channel blockers	467 (19.2)	111 (18.6)	200 (18.4)	117 (20.4)	39 (23.4)
Diuretics	500 (20.6)	99 (16.6)	198 (18.2)	162 (28.3)	41 (24.6)
Diabetes,[f] no. (%)	449 (18.5)	0	98 (9.0)	225 (39.3)	126 (75.4)
Plasma glucose,[g] mmol/L	6.0 ± 2.0	5.4 ± 1.0	5.7 ± 1.4	6.7 ± 2.4	8.2 ± 3.2

Table 1: Continued

Glucose lowering drugs,[h] no. (%)	320 (13.2)	0	72 (6.6)	169 (29.5)	79 (47.3
Oral glucose lowering drugs	253 (10.4)	0	56 (5.1)	135 (23.6)	62 (37.1)
Insulin analogues	107 (4.4)	0	25 (2.3)	52 (9.1)	30 (18.0)
Serum LDL,[i] mmol/L	2.74 ± 0.80	2.68 ± 0.81	2.74 ± 0.79	2.75 ± 0.79	2.86 ± 0.87
Lipid modifying drugs,[j] no. (%)	2089 (86.1)	518 (86.6)	938 (86.2)	485 (84.6)	148 (88.6)
Statins	2073 (85.4)	516 (86.3)	933 (85.8)	478 (83.4)	146 (87.4)
Anti-thrombotic agents,[k] no. (%)	2368 (97.6)	583 (97.5)	1060 (97.4)	560 (97.7)	165 (98.8)
Serum hsCRP, mg/L	1.7 (0.8–3.6)	1.2 (0.6–2.8)	1.5 (0.8–3.3)	2.3 (1.1–4.6)	2.9 (1.2–5.2)
Serum cystatin C, mg/L	0.97 ± 0.24	0.93 ± 0.20	0.97 ± 0.24	1.01 ± 0.28	0.97 ± 0.24
Serum creatinine,[l] µmol/L	90.1± 29.3	89.2 ± 25.0	90.0 ± 30.4	92.7 ± 32.1	82.1 ± 26.1
$eGFR_{cysC}$,[m] mL/min/1.73m^2	81.5 ± 19.5	84.9 ± 17.9	81.0 ± 19.3	78.7 ± 20.8	81.7 ± 20.5
$eGFR_{cr\text{-}cysC}$,[m] mL/min/1.73m^2	78.5 ± 18.7	80.8 ± 17.1	78.4 ± 18.6	75.8 ± 19.8	80.1 ± 19.7

ACE, angiotensin-converting enzyme; ATII, angiotensin II; cr, creatinine; cysC, cystatin C; eGFR, estimated glomerular filtration rate; LDL, low-density lipoprotein; MI, myocardial infarction.
Data are reported as number of patients (%), mean ± SD or median (interquartile range).
[a] Higher vocational education or university.
[b] At least 1 glass/week.
[c] Body mass index ≥30 kg/m^2.
[d] Systolic blood pressure of ≥140 mmHg and/or diastolic blood pressure of ≥90 mmHg, irrespective of use of blood pressure lowering drugs.
[e] Blood pressure-lowering drugs: Anatomical Therapeutic Chemical Classification System (ATC) codes C02, C03, C07, C08, and C09.
[f] Self-reported diagnosis by a physician, use of glucose-lowering drugs, or hyperglycemia.
[g] To convert the values for glucose to mg/dL, divide by 0.05551.
[h] Glucose lowering drugs: ATC code A10, A10A, A10B, A10X.
[i] To convert the values for LDL-cholesterol to mg/dL, divide by 0.02586.
[j] Lipid-modifying drugs: ATC code C10, C10AA.
[k] Anti-thrombotic agents: ATC code B01.
[l] To convert the values for creatinine to mg/dL, divide by 88.40.
[m] $eGFR_{cysC}$ and $eGFR_{cr\text{-}cysC}$ based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations from 2012.

Kidney function decline

After 41 months of follow-up mean [95%-confidence interval (CI)] $eGFR_{cysC}$ decline for all patients was -4.62 (-5.06; -4.18) mL/min/1.73m^2, corresponding to an annual decline of -1.34 (-1.47; -1.21) mL/min/1.73m^2. Men and women had annual kidney function decline rates of -1.45 (-1.59; -1.31) and -0.91 (-1.19; -0.63) mL/min/1.73m^2, respectively. Patients younger than 70 years *vs* 70 years or older had annual kidney function decline rates of -1.15 (-1.32; -0.98) and -1.60 (-1.80; -1.41) mL/min/1.73m^2, respectively. After multivariable adjustment (model 2), patients without or with diabetes had an annual $eGFR_{cysC}$ decline of -1.17 (-1.31; -1.03) and -2.07 (-2.37; -1.78) mL/min/1.73m^2 [difference -0.90 (-1.23; -0.57)] (Table 2). Patients with normal or high blood pressure had annual decline rates of -1.01 (-1.20; -0.82) and -1.51 (-1.69; -1.34) mL/min/1.73m^2 [difference -0.50 (-0.76; -0.24)]. Successive quartiles of systolic blood pressure (quartile ranges: 86.5 to 128.0; 128.5 to141.5; 142.0 to 156.5; 157.0 to 237.5 mmHg) showed a faster annual kidney function decline: -0.99 (-1.25; -0.74), -1.10 (-1.34; -0.85), -1.45 (-1.70; -1.20) and -1.82 (-2.07; -1.57) mL/min/1.73m^2, respectively. Each 10 mmHg systolic blood pressure increment was associated with an extra annual kidney function decline of -0.17 (-0.23; -0.12, P<0.001) mL/min/1.73m^2. We found a weak U-shaped relation between diastolic blood pressure and kidney function decline. Annual kidney function decline for patients in the lowest through the highest quartile was -1.33 (-1.59; -1.08), -1.15 (-1.40; -0.91), -1.32 (-1.58; -1.06) and -1.55 (-1.80; -1.30) mL/min/1.73m^2 (quartile ranges: 44.0 to 73.5; 74.0 to 81.0; 81.5 to 88.0; 88.5 to 124.0 mmHg). We found no significant difference in the rate of annual kidney function decline between patients with high compared to normal LDL levels. Smokers of cigarettes compared to non-smokers had an additional annual $eGFR_{cysC}$ decline of -0.19 (-0.54; 0.16) mL/min/1.73m^2. Obesity was associated with a 23% faster kidney function decline (Table 2). We found no evidence for effect modification between sex, age, strata of baseline kidney function and the pre-specified cardiovascular risk factors with regard to $eGFR_{cysC}$ decline.

Of all patients, 573 (24.4%) had a rapid kidney function decline. Table 3 shows the odds ratios (OR) for rapid kidney function decline according the a priori selected cardiovascular risk factors. Especially, diabetes [OR 1.72 (1.36; 2.17)] and high blood pressure [OR 1.43 (1.18; 1.74)] were strongly associated with rapid kidney function decline. Associations for current smoking [OR 1.21 (0.94; 1.57)] and obesity [OR 1.15 (0.92; 1.45)] were weaker. High LDL was associated with slower kidney function decline [OR 0.80 (0.66; 0.98)]. Results were comparable when defining rapid kidney function decline as >5 mL/min/1.73m^2 per year (data not shown). Furthermore, after adjustment for age and treatment group, men had a slightly higher risk on rapid kidney function decline than women [OR 1.13 (0.89; 1.43)]. After adjustment for sex and treatment group, older compared to younger patients had more often rapid kidney function decline [age ≥70y *vs* <70y OR 1.32 (1.09; 1.59), age ≥75y *vs* <75y OR 1.59 (1.25; 2.02)].

Table 2: Mean (95%-CI) annual cystatin C-based eGFR decline rates in 2426 post-MI patients according to absence or presence of cardiovascular risk factors.

Risk factor		n	Crude	Model 1	Model 2
Diabetes	No (ref)	1977	-1.17 (-1.31; -1.03)	-1.17 (-1.31; -1.03)	-1.17 (-1.31; -1.03)
	Yes	449	-2.06 (-2.36; -1.77)**	-2.10 (-2.40; -1.81)**	-2.07 (-2.37; -1.78)**
Blood pressure	<140/90 mmHg (ref)	1062	-1.01 (-1.20; -0.82)	-1.01 (-1.20; -0.82)	-1.01 (-1.20; -0.82)
	≥140/90 mmHg	1364	-1.59 (-1.76; -1.42)**	-1.51 (-1.69; -1.34)**	-1.51 (-1.69; -1.34)**
Serum LDL	<2.5 mmol/L (ref)	990	-1.47 (-1.67; -1.27)	-1.47 (-1.67; -1.27)	-1.47 (-1.67; -1.27)
	≥2.5 mmol/L	1436	-1.25 (-1.41; -1.08)	-1.29 (-1.46; -1.12)	-1.28 (-1.45; -1.12)
Cigarette smoking	Non-smoking (ref)	2040	-1.32 (-1.46; -1.18)	-1.32 (-1.46; -1.18)	-1.32 (-1.46; -1.18)
	Currently smoking	386	-1.43 (-1.75; -1.11)	-1.54 (-1.86; -1.22)	-1.51 (-1.83; -1.18)
Body mass index	<30.0 kg/m^2 (ref)	1871	-1.30 (-1.45; -1.16)	-1.30 (-1.45; -1.16)	-1.30 (-1.45; -1.16)
	≥30.0 kg/m^2	555	-1.46 (-1.72; -1.19)	-1.62 (-1.89; -1.35)*	-1.61 (-1.88; -1.34)

CI, confidence interval; LDL, low-density lipoprotein.
Adjusted variables were fixed at the mean value of the reference group, hence the estimates of the reference category are equal across models. Diabetes was defined as self-reported diagnosis by a physician, use of glucose-lowering drugs, or in case of elevated plasma glucose level
* p<0.05, ** p<0.001 for difference between presence vs absence of risk factor.
Model 1: adjusted for age, sex and treatment group.
Model 2: Model 1 plus additional adjustment for current smoking, alcohol consumption, level of education, diabetes, high blood pressure, high LDL, and obesity. Analyses for obesity were not adjusted for diabetes, high blood pressure, and high LDL.

Table 3: Odds ratios (95%-CI) for risk of rapid $eGFR_{cysC}$ decline (>3 mL/min/1.73m² per year) in 2426 post-MI patients, for different cardiovascular risk factors.

Risk factor¶	Crude	Model 1	Model 2
Diabetes	1.77 (1.41; 2.21)**	1.79 (1.43; 2.25)**	1.72 (1.36; 2.17)**
High blood pressure	1.48 (1.22; 1.79)**	1.41 (1.17; 1.72)**	1.43 (1.18; 1.74)**
High LDL	0.81 (0.67; 0.98)*	0.82 (0.68; 0.99)*	0.80 (0.66; 0.98)*
Current cigarette smoking	1.13 (0.88; 1.45)	1.23 (0.95; 1.58)	1.21 (0.94; 1.57)
Obesity	1.09 (0.88; 1.36)	1.17 (0.93; 1.46)	1.15 (0.92; 1.45)

CI, confidence interval; LDL, low-density lipoprotein.
* p<0.05, ** p<0.001
¶ Reference: absence of the risk factor of interest.
Diabetes was defined as self-reported diagnosis by a physician, use of glucose-lowering drugs, or hyperglycemia. High blood pressure was defined as systolic blood pressure of ≥140 mmHg and/or diastolic blood pressure of ≥90 mmHg, irrespective of use of blood pressure lowering drugs. High LDL was defined as serum LDL level ≥2.5 mmol/L. Obesity was defined as BMI ≥30.0 kg/m².
Model 1: adjusted for age, sex and treatment group.
Model 2: Model 1 plus additional adjustment for current smoking, alcohol consumption, level of education, diabetes, high blood pressure, high LDL, and obesity. Analyses for obesity were not adjusted for diabetes, high blood pressure, and high LDL.

Kidney function decline and number of risk factors

We calculated the annual kidney function decline and risk for rapid kidney function decline in each patient according to the number of cardiovascular risk factors; diabetes, high blood pressure, current smoking of cigarettes and obesity (BMI ≥ 30kg/m²). Patients without any of these cardiovascular risk factors present (thus with optimal cardiovascular parameters and healthy lifestyle) had an annual kidney function decline of -0.90 (-1.16; -0.65) mL/min/1.73m² (Table 4, Figure 1). Each additional cardiovascular risk factor was associated with a progressively faster annual kidney function decline [linear regression coefficient -0.45 (-0.59; -0.30) per additional risk factor, P for linear trend <0.001)]. Patients in whom three or more cardiovascular risk factors were present had an annual kidney function decline of -2.37 (-2.85; -1.89) mL/min/1.73m². Risk for rapid kidney function decline increased progressively with every additional cardiovascular risk factor (Table 4, Figure 1). Patients with at least three cardiovascular risk factors had a 2.5-fold increased risk compared to patients without any cardiovascular risk factor. Patients in whom all four cardiovascular risk factors (n=16) were present, had an annual kidney function decline of -4.59 (-5.38; -3.79) mL/min/1.73m².

Table 4: Mean (95%-CI) annual $eGFR_{cysC}$ decline and odds ratios (95%-CI) for rapid $eGFR_{cysC}$ decline (>3 mL/min/1.73m² per year) are presented per number of cardiovascular risk factors¶, in 2426 post-MI patients of the Alpha Omega cohort.

Number of risk factors¶	n		Crude	Model 1	Model 2
0 (ref)	597	Annual $eGFR_{cysC}$ decline	-0.90 (-1.16; -0.65)	-0.90 (-1.16; -0.65)	-0.90 (-1.16; -0.65)
1	1088		-1.29 (-1.48; -1.10)	-1.23 (-1.42; -1.03)	-1.23 (-1.42; -1.03)
2	574		-1.61 (-1.87; -1.35)	-1.66 (-1.92; -1.40)	-1.65 (-1.91; -1.39)
≥3	167		-2.26 (-2.74; -1.77)	-2.37 (-2.85; -1.88)	-2.37 (-2.85; -1.89)
0 (ref)	597	OR rapid decline	1	1	1
1	1088		1.14 (0.89; 1.46)	1.09 (0.85; 1.40)	1.09 (0.85; 1.40)
2	574		1.55 (1.18; 2.03)	1.57 (1.19; 2.06)	1.56 (1.19; 2.06)
≥3	167		2.41 (1.66; 3.49)	2.55 (1.77; 3.71)	2.55 (1.75; 3.71)

CI, confidence interval; OR, Odds ratio.
Adjusted variables were fixed at the mean value of the reference group, hence the estimates of the reference category are equal across models.
¶ Cardiovascular risk factors included: diabetes, high blood pressure, obesity, current smoking.
Diabetes was defined as self-reported diagnosis by a physician, use of glucose-lowering drugs, or hyperglycemia. High blood pressure was defined as systolic blood pressure of ≥140 mmHg and/or diastolic blood pressure of ≥90 mmHg, irrespective of use of blood pressure lowering drugs. Obesity was defined as BMI ≥30.0 kg/m².
Model 1: adjusted for age, sex and treatment group.
Model 2: Model 1 plus additional adjustment for alcohol consumption and level of education.

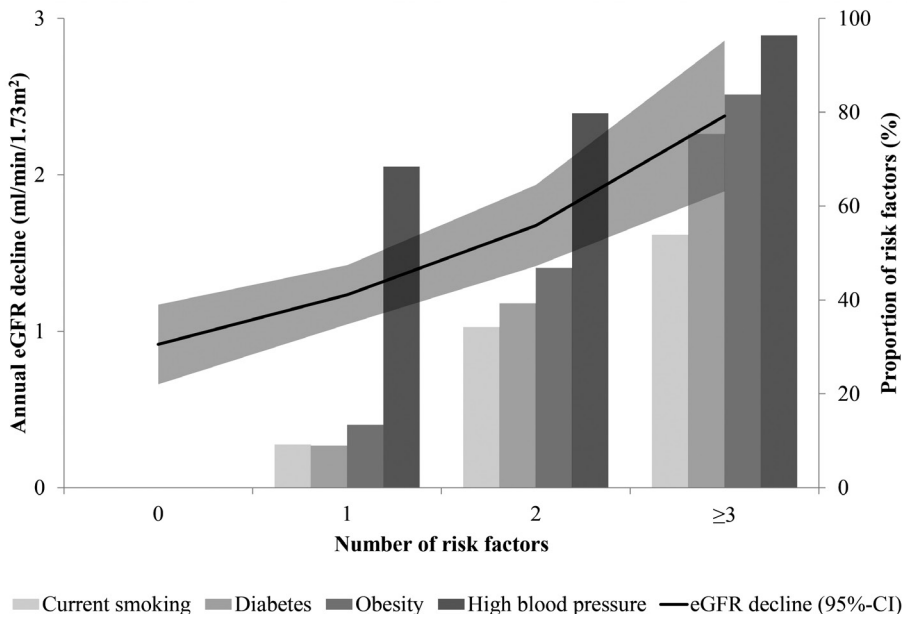

Figure 1: Annual $eGFR_{cysC}$ decline according to the number of cardiovascular risk factors, in 2426 post-MI patients in the Alpha Omega cohort. For the four groups according to the number of cardiovascular risk factors (diabetes, high blood pressure, obesity, and current smoking) the proportion (%) of the four different risk factors (columns, right vertical axis) and the mean (95%-CI) annual $eGFR_{cysC}$ decline (black line, left vertical axis), adjusted for age, sex, and treatment group are presented.

SENSITIVITY ANALYSES

Results did not materially change when using complete cases only, instead of multiple imputed data. Adjustment with continuous instead of dichotomized variables did not change the results. Adjustment for time since MI, serum hsCRP, or use of RAS blocking drugs yielded similar results. Confining analyses to patients who persistently used RAS blocking drugs (n=1206), yielded comparable associations. Analyses based on $eGFR_{cr\text{-}cysC}$ as outcome showed slightly weaker effect estimates (Supplementary Table S1 and S2). The association between the number of cardiovascular risk factors and annual $eGFR_{cr\text{-}cysC}$ or $eGFR_{cysC}$ decline was comparable (Supplementary Table S3).

DISCUSSION

We showed in a cohort of stable older post-MI patients, that those patients with optimally treated cardiovascular risk factors, including healthy lifestyle, had an annual kidney function decline of about -0.90 mL/min/1.73m^2. In contrast, post-MI patients with three or more suboptimal treated cardiovascular risk factors, had a 2.5-fold faster annual kidney function decline of about -2.37 mL/min/1.73m^2. We recently showed that in these post-MI patients, an $eGFR_{cysC}$ below 80 mL/min/1.73m^2 is a graded risk factor for cardiovascular and all-cause mortality, underlining the clinical relevance of these findings.[2, 28]

The mean annual kidney function decline of -0.90 (-1.16; -0.65) mL/min/1.73m^2 that we found in optimally treated cardiac patients with healthy lifestyle, is within the normal range of the age-related kidney function decline in healthy individuals of -1.0 mL/min/1.73m^2.[32-34] The mean (95%-CI) annual kidney function decline of all patients was -1.34 (-1.47; -1.21) mL/min/1.73m^2. Previously, the PREVEND study reported in post-MI patients an annual kidney function decline (95%-CI) of -2.2 (-5.0; -0.9) mL/min/1.73m^2.[5] Post-MI patients of the PREVEND study had a similar cardiovascular risk profile compared to patients of the Alpha Omega cohort. There are several explanations that may have resulted in the higher annual kidney function decline in the PREVEND compared to the Alpha Omega cohort. First, the small number (n=66) of post-MI patients in the PREVEND study resulted in a wide 95%-confidence interval and as a consequence the effect-estimate is less precise. Patients from the Alpha Omega cohort participated in a trial for 41 months. Trial patients generally are healthier and more compliant compared to the general population, a phenomenon known as volunteer bias.[35] Finally, during follow-up patients in the Alpha Omega cohort (2002 to 2009) have been more strictly controlled according to more recent secondary prevention guidelines, compared to patients in the PREVEND cohort (1997 to 2005). In updated guidelines there was especially more attention for patient education, lifestyle monitoring (e.g. smoking cessation, weight management), diabetes and high blood pressure management, more strict lipid regulation and standard prescription of statins and ACE-inhibitors.[36, 37]

In agreement with other studies, we found that diabetes and high blood pressure were strongly associated with accelerated kidney function decline.[7-10] Diabetes may lead to diabetic nephropathy; a complex disease characterized by hemodynamic, metabolic, and inflammatory changes, ultimately leading to progressive interstitial fibrosis and glomerular damage.[38] High blood pressure may cause increased intraglomerular pressure, leading to endothelial dysfunction, loss of adequate auto-regulation and eventually to progressive glomerular and interstitial fibrosis.[39] We found a weak association between high LDL level and slower kidney function decline, but this association may be distorted by the fact that 85% of all patients used statins.

Moreover, of all patients with high LDL at baseline, 10% started with a statin during follow-up. Our finding is in concordance with recent guidelines, stating that CKD patients ≥50y should be treated with a statin independent of lipid levels without trying to reach a target level.[40] This paradigm shift is caused by the lack of evidence linking changes in lipid levels with actual cardiovascular risk and emerging evidence showing pleiotropic effects of statins.[30, 41, 42]

In line with other studies, we found that obesity was associated with faster kidney function decline.[8, 43] Obesity promotes deterioration of kidney function through cardiovascular risk factors, such as diabetes and hypertension, and is also associated with visceral fat accumulation and accompanying inflammation, leading to glomerular and interstitial fibrosis.[12, 13, 24] Furthermore, we found that smoking of cigarettes was associated with kidney function decline, which is confirmed by other studies. [44] However, the association of smoking and kidney function decline was weaker than expected; and could be underestimated due to underreporting, so called information bias.

Our study has some limitations. First, the observational design prevents us from making causal inferences. Second, kidney function was estimated at only two time points and was not directly measured. Third, we had no information about proteinuria, an important independent predictor of kidney function. Therefore, we could not study the association between optimal treatment of cardiovascular risk factors and change of proteinuria. Fourth, about 17% of patients dropped out owing to missing samples, refused participation, or death. If anything, this may have resulted in underestimation of the associations that we found, since patients who dropped-out were most likely less healthy. Fifth, volunteer bias may be present, since we only included trial patients. However, since volunteering patients usually are more healthy, we expect this may have led to an underestimation of our results. Finally, we analyzed post-MI patients only, which may hamper generalizability of our results. Notably, the prevalence of cardiovascular disease shows an increasing trend worldwide, our cohort of patients therefore represents a growing patient group.

A major strength of this study is our large homogeneous population of post-MI patients, which provides a unique opportunity to study the course of kidney function decline in these patients. Second, we used both $eGFR_{cysC}$ and $eGFR_{cr\text{-}cysC}$ as outcome, currently the most accurate available methods to estimate kidney function.[26, 28, 45]

To conclude, we found a faster rate of kidney function decline in post-MI patients with an increasing number of insufficiently treated cardiovascular risk factors (including unhealthy lifestyle). Post-MI patients with optimal cardiovascular and lifestyle parameters have an annual kidney function decline comparable to the general population. Further research is needed to investigate whether optimization of cardiovascular risk factors and healthy lifestyle may slow down the accelerated kidney function decline in post-MI patients.

ACKNOWLEDGEMENTS

The Alpha Omega Cohort Study is registered at ClinicalTrials.gov (no. NCT03192410). Results from this study have been previously presented at the ERA-EDTA Congress in Madrid, June 2017 (poster 55-SP) and at the Dutch Nephrology Days (NND) March 2017.

DISCLOSURES

EH is a member of the Guideline Committee of the Dutch Federation of Nephrology. JG received research funding from Unilever R&D for epidemiological studies of dietary fatty acids and is a member of the Standing Committee on Nutrition of the Dutch Health Council, Working Group on Minerals of the European Food and Safety Authority, and Dutch Academy for Nutritional Sciences, and is a Fellow of the American Heart Association. DK received research funding from the Royal Netherlands Academy of Arts and Sciences and is Member of the Dutch Academy of Nutritional Sciences. KE, JF, and EG report that they have no disclosures.

FUNDING

Financial support was obtained from the Dutch Kidney Foundation (PV41; EH), the Dutch Heart Foundation (JG and DK) and the National Institutes of Health (JG and DK). The grant from the Dutch Kidney Foundation covered baseline and final examinations of kidney function. The grant from the Dutch Heart Foundation covered baseline examinations. The grant from the National Institutes of Health covered final examinations.

AUTHORS' CONTRIBUTIONS

KE, JG, DK and EH contributed to conception and design of the manuscript. KE, JG, EG, DK and EH contributed to acquisition, analysis and interpretation, and drafted the manuscript. JF contributed to interpretation. All authors critically revised the manuscript, all gave final approval and all agreed to be accountable for all aspects of work, ensuring integrity and accuracy.

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SUPPLEMENTARY DATA

Table S1: Mean (95%-CI) annual creatinine cystatin C-based eGFR decline rates in 2344 post-MI patients according to absence or presence of cardiovascular risk factors.

Risk factor		n	Crude	Model 1	Model 2
Diabetes	No (ref)	1906	-1.59 (-1.75; -1.42)	-1.59 (-1.75; -1.42)	-1.59 (-1.75; -1.42)
	Yes	438	-2.38 (-2.73; -2.03)*	-2.36 (-2.71; -2.01)*	-2.34 (-2.69; -1.98)*
Blood pressure	<140/90 mmHg (ref)	1026	-1.43 (-1.66; -1.20)	-1.43 (-1.66; -1.20)	-1.43 (-1.66; -1.20)
	≥140/90 mmHg	1318	-1.97 (-2.18; -1.77)*	-1.94 (-2.14; -1.73)*	-1.95 (-2.15; -1.74)*
Serum LDL	<2.5 mmol/L (ref)	957	-1.85 (-2.09; -1.61)	-1.85 (-2.09; -1.61)	-1.85 (-2.09; -1.61)
	≥2.5 mmol/L	1387	-1.66 (-1.85; -1.46)	-1.66 (-1.86; -1.46)	-1.66 (-1.86; -1.46)
Cigarette smoking	Non-smoking (ref)	1983	-1.73 (-1.89; -1.56)	-1.73 (-1.89; -1.56)	-1.73 (-1.89; -1.56)
	Currently smoking	361	-1.77 (-2.15; -1.38)	-1.83 (-2.22; -1.44)	-1.80 (-2.19; -1.41)
Body mass index	<30.0 kg/m^2 (ref)	1814	-1.68 (-1.86; -1.51)	-1.68 (-1.86; -1.51)	-1.68 (-1.86; -1.51)
	≥30.0 kg/m^2	530	-1.91 (-2.23; -1.59)	-1.95 (-2.27; -1.62)	-1.93 (-2.26; -1.61)

CI, confidence interval; LDL, low-density lipoprotein.
Adjusted variables were fixed at the mean value of the reference group, hence the estimates of the reference category are equal across models. Diabetes was defined as self-reported diagnosis by a physician, use of glucose-lowering drugs, or hyperglycemia.
* p<0.001 for difference between presence *vs* absence of risk factor.
Model 1: adjusted for age, sex and treatment group.
Model 2: Model 1 plus additional adjustment for current smoking, alcohol consumption, level of education, diabetes, high blood pressure, high LDL, and obesity. Analyses for obesity were not adjusted for diabetes, high blood pressure, and high LDL.

Table S2: Odds ratios (95%-CI) for risk of rapid creatinine cystatin C-based eGFR decline (>3 mL/min/1.73m² per year) in 2344 post-MI patients, for different cardiovascular risk factors.

Risk factor ¶	Crude	Model 1	Model 2
Diabetes	1.28 (1.04; 1.59)*	1.27 (1.02; 1.58)*	1.24 (0.99; 1.54)
High blood pressure	1.30 (1.09; 1.54)*	1.28 (1.07; 1.52)*	1.31 (1.10; 1.56)*
High LDL	0.81 (0.68; 0.96)*	0.81 (0.68; 0.96)*	0.80 (0.67; 0.95)*
Current cigarette smoking	0.90 (0.71; 1.14)	0.93 (0.73; 1.18)	0.92 (0.72; 1.17)
Obesity	1.07 (0.87; 1.31)	1.06 (0.86; 1.31)	1.05 (0.85; 1.29)

CI, confidence interval; LDL, low-density lipoprotein, eGFR, estimated glomerular filtration rate.
* p<0.05
¶ Reference: absence of the risk factor of interest.
Diabetes was defined as self-reported diagnosis by a physician, use of glucose-lowering drugs, or hyperglycemia. High blood pressure was defined as systolic blood pressure of ≥140 mmHg and/or diastolic blood pressure of ≥90 mmHg, irrespective of use of blood pressure lowering drugs. High LDL was defined as serum LDL level ≥2.5 mmol/L. Obesity was defined as BMI ≥30.0 kg/m².
Model 1: adjusted for age, sex and treatment group.
Model 2: Model 1 plus additional adjustment for current smoking, alcohol consumption, level of education, diabetes, high blood pressure, high LDL, and obesity. Analyses for obesity were not adjusted for diabetes, high blood pressure, and high LDL.

Table S3: Mean (95%-CI) annual creatinine cystatin C-based eGFR decline and odds ratios (95%-CI) for rapid creatinine cystatin C-based eGFR decline (>3 mL/min/1.73m² per year) per number of cardiovascular risk factors¶, in 2344 post-myocardial infarction patients of the Alpha Omega cohort.

Number of risk factors¶	n		Crude	Model 1	Model 2
0 (ref)	581	Annual $eGFR_{cr-cysC}$	-1.33 (-1.63; -1.02)	-1.33 (-1.63; -1.02)	-1.33 (-1.63; -1.02)
1	1051	decline	-1.72 (-1.95; -1.50)	-1.69 (-1.92; -1.46)	-1.69 (-1.92; -1.46)
2	554		-1.88 (-2.19; -1.57)	-1.87 (-2.18; -1.56)	-1.87 (-2.18; -1.55)
≥3	158		-2.83 (-3.41; -2.24)	-2.84 (-3.43; -2.26)	-2.85 (-3.44; -2.27)
0 (ref)	581	OR rapid decline	1	1	1
1	1051		1.03 (0.83; 1.28)	1.01 (0.81; 1.25)	1.00 (0.81; 1.25)
2	554		1.19 (0.93; 1.52)	1.17 (0.91; 1.50)	1.16 (0.90; 1.48)
≥3	158		1.57 (1.09; 2.25)	1.56 (1.08; 2.24)	1.56 (1.08; 2.24)

CI, confidence interval; OR, Odds ratio; eGFR, estimated glomerular filtration rate.
Adjusted variables were fixed at the mean value of the reference group, hence the estimates of the reference category are equal across models.
¶ Cardiovascular risk factors included: diabetes, high blood pressure, obesity, current smoking.
Diabetes was defined as self-reported diagnosis by a physician, use of glucose-lowering drugs, or hyperglycemia. High blood pressure was defined as systolic blood pressure of ≥140 mmHg and/or diastolic blood pressure of ≥90 mmHg, irrespective of use of blood pressure lowering drugs. Obesity was defined as BMI ≥30.0 kg/m².
Model 1: adjusted for age, sex and treatment group.
Model 2: Model 1 plus additional adjustment for alcohol consumption and level of education

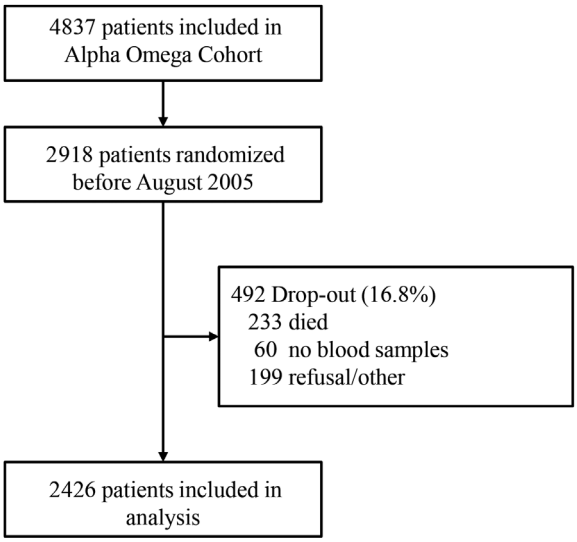

Figure S1: Flow chart of 2426 post-MI patients included in the present study. The patients randomized before August 2005 are considered a random sample of the total population of 4837 patients. Of all deceased patients, 3 died of renal failure.