Consumption of whole grains, fruit and vegetables is not associated with indices of renal function in the population-based longitudinal Doetinchem study

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Abstract

Emerging evidence suggests that diet and renal function are related. Little is known, however, about the association of consumption of whole grains, fruit and vegetables with urinary albumin:creatinine ratio (ACR) and changes in estimated glomerular filtration rate (eGFR). We investigated this in a population-based cohort aged 26–65 years. Data were from 3787 participants from the Doetinchem cohort study, who were examined ≥3 times, 5 years apart. Consumption of food groups was assessed at each round with a validated FFQ. GFR was estimated at each round from routinely measured cystatin C and creatinine using the Chronic Kidney Disease-Epidemiology (CKD-EPI) equation. ACR was measured at the last round. Generalised estimated equation models were performed to examine associations with changes in eGFR. Linear regression was used to examine associations with ACR. Adjustments were made for covariates related to lifestyle, biological factors and diet. Mean baseline eGFR was 104·5 (sd 13·7) and mean annual decline was −0·95 (sd 0·67) ml/min per 1·73 m² over a 15-year follow-up. A trend was observed towards slightly less annual decline in eGFR among those with higher consumption of whole grains ($P = 0.06$). This association, however, was attenuated and no longer significant in multivariate models ($P = 0.29$). Consumption of fruit and vegetables was not associated with changes in eGFR and urinary ACR. In conclusion, consumption of whole grains, fruit and vegetables is not associated with changes in eGFR and mean ACR. As this was the first longitudinal study into this association in the general population, and as results are only partially in line with related studies, further research is recommended.

Key words: Food groups: Renal function: Longitudinal studies: Population-based cohorts: Epidemiology

Chronic kidney disease (CKD) is increasingly recognised as a major global public health problem[1]. Patients with CKD are at an increased risk for CVD, end-stage renal disease and all-cause mortality. Primary prevention of CKD is therefore clearly an important public health priority.

One modifiable factor that could reduce the risk of CKD may be diet. Evidence suggests that diets low in animal protein, animal fat, cholesterol and Na and high in β-carotene may be protective against renal dysfunction[2]. However, as the examination of nutrients only is unlikely to completely reflect health effects of diet, studying food groups may be a useful complementary approach. We recently found that coffee consumption was associated with a slightly higher estimated glomerular filtration rate (eGFR; lower eGFR may be a marker of renal damage)[3]. We also found a higher low-fat dairy product consumption to be associated with less annual decline in eGFR[4]. A link between consumption of whole grains, fruit and vegetables, for instance, and renal function may be plausible too, as these food groups have earlier been associated with type 2 diabetes and CVD, which are related to renal dysfunction[5–9]. Indeed, cross-sectional findings from the Multi-Ethnic Study of Atherosclerosis (MESA) showed that higher consumption of whole grains and fruit was associated with lower albumin:creatinine ratio (ACR; greater ACR may be a marker of renal damage)[10]. These associations may partly be attributable to major components of these food groups, such as fibre, Mg, antioxidants and several B vitamins[11–14].

Until now, only two longitudinal studies reported on the associations of these food groups with indices of renal function, and their findings are inconsistent. In the Northern Manhattan Study (NOMAS), a high consumption of vegetables was associated with decreased risk of incident low (<60 ml/min per $1.73 m^2$) eGFR[15]. The Framingham Heart Study (FHS), however, found no associations between consumption of whole grains, fruit and vegetables and microalbuminuria (moderate increase of albumin excretion in the urine, which is a predictor of poor renal outcomes), incident low eGFR or risk of rapid eGFR decline (loss of >3 ml/min per $1.73 m^2$/year)[16]. However, both study populations comprised relatively older men and women and mostly had a mildly impaired eGFR (<90 ml/min per $1.73 m^2$) at baseline. Furthermore, serum creatinine was available at only two time points 10 years apart, which did not allow for accurate assessment of annual rate of renal function decline.

In the present study, we therefore aim to investigate associations between consumption of whole grains, fruit and vegetables and decline of the eGFR, in a population-based cohort of adults, with 5-yearly repeated measurements of all variables, over 15 years of follow-up. We will also study associations between consumption of these food groups and ACR. Furthermore, we will examine whether possible associations are mediated through increased fibre, Mg, antioxidant and/or B vitamins intake.

Methods

Study setting

The Doetinchem Cohort Study is a Dutch prospective population-based study on factors affecting the health and well-being of Dutch adults. The first examination round (1987–1991; R1) was carried out among 12 405 men and women aged 20–59 years from the town of Doetinchem. Because of the extension of the study protocol, with similar budget, not all 12 405 participants could be re-invited. Instead, of those, a random sample of 7768 was re-invited to be examined in 1993–1997 (R2, *n* 6113), 1998–2002 (R3, *n* 4916), 2003–2007 (R4, *n* 4520) and 2008–2012 (R5, *n* 4017). The study was approved by an ethical review board, and informed consent was received from all participants. Further details of the study design have been described elsewhere[17].

Study population

For the analysis with changes in eGFR as the outcome, we included those who responded to R2 in 1993–1997 (*n* 6113), because data on diet and eGFR were not available before 1993. For the analysis with ACR as the outcome, we included those who responded to R4 in 2003–2007 (*n* 4520), and who had ACR measured in R5 in 2008–2011, giving a total of 1929 participants. ACR data were not available before 2008 and after 2012. Pregnant women were censored at the round in which they reported to be pregnant. Furthermore, for both analyses we excluded participants as indicated in Fig. 1.

Dietary assessment

Diet was assessed at R2–R4, using a self-administered semi-quantitative validated FFQ, which was developed for the European Prospective Investigation into Cancer and Nutrition study. Participants reported their usual frequency of consumption of 178 food and beverage items over the past 12 months, partially supported by coloured photographs. Consumption of food and beverage items (in g/d) and nutrient intakes were calculated using an extended version of the Dutch Food
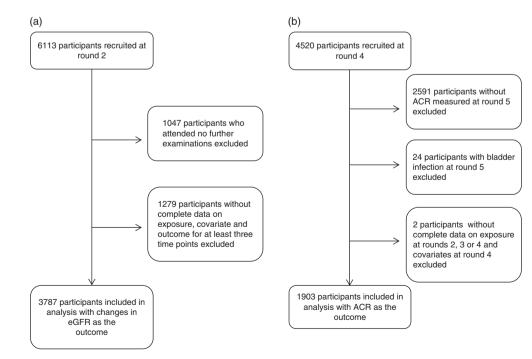

Fig. 1. Flow diagram of (a) analysis of consumption of whole grains, fruit and vegetables and changes in estimated glomerular filtration rate (eGFR), and (b) analysis of consumption of whole grains, fruit and vegetables and albumin:creatinine ratio (ACR).

Composition database of 1996[18]. Total vegetable consumption included intake of chicory, endive, lettuce, spinach, cucumbers, butter beans, bell peppers, tomatoes, carrots, red beets, cabbages, mushrooms, green beans, spring beans, onions, garlic, stalk vegetables, sprouts and green peas. We did not consider potatoes as vegetables, as their nutritional value differs significantly from that of vegetables. Consumption of fruit comprised intake of applesauce, apples, pears, bananas, cherries, citrus fruits, grapes, kiwis, melons, peaches and strawberries. Fruit and vegetable juices were not included as they differ from their source of origin in terms of added sugar and food matrix[19]. Unfortunately, our FFQ could not distinguish 100% fruit and vegetable juices from other juices. Whole grains were defined as wholemeal bread, rye bread and unrefined grains (e.g. brown rice)[20].

The Spearman correlation coefficients for reproducibility after 12 months were 0·76 in men and 0·65 in women for vegetable intake, 0·61 in men and 0·77 in women for fruit intake and 0·86 in men and 0·85 in women for bread intake (as a proxy for whole grains)[21]. Furthermore, the validity was tested against twelve repeated 24-h recalls. Pearson's correlation coefficients were 0·31 in men and 0·38 in women for vegetables, 0·68 in men and 0·56 in women for fruit and 0·76 in men and 0·78 in women for bread. Furthermore, the tracking coefficients covering a 15-year period were found to be moderate for whole grains (0·47), fruit (0·61) and vegetable (0·51) consumption (all $P < 0.001$)[22].

Assessment of renal function

In all rounds, trained staff collected 30-ml non-fasting plasma blood samples. Cystatin C was measured by particle-enhanced turbidimetric immunoassay using reagents from Gentian (Gentian), with intra-assay and interassay CV of <4·1 and 3·3%, respectively. Serum creatinine was measured by dry chemistry (Eastman Kodak), with intra-assay and interassay CV of 0·9 and 2·9%, respectively. All available samples for each participant from successive rounds were measured in a single run in 2012, which optimally reduced the interassay variation[23]. We estimated GFR using the Chronic Kidney Disease-Epidemiology (CKD-EPI) creatinine–cystatin C equation (2012), as both serum creatinine and cystatin C more accurately estimated renal function compared with models that included creatinine and cystatin C alone[24]. Annual decline of eGFR was calculated by subtracting eGFR between successive examinations and dividing by five, as each round was approximately 5 years apart. Urinary albumin and creatinine were assessed from spot urine samples obtained at R5. Albumin was measured by nephelometry, with intra-assay and interassay CV of 2·2 and 2·6%, respectively (Dade Behring Diagnostic). Urinary creatinine was assessed by Kodak Ektachem dry chemistry (Eastman Kodak). Intra-assay and interassay CV were 0·9 and 2·9%, respectively. ACR was determined from urinary albumin and creatinine and expressed as mg/g.

Covariates

Data on socio-demographic, lifestyle, medical history of chronic diseases and medication use were collected at each round. Education was assessed as the highest level attained over follow-up and classified into low (intermediate secondary education or less), intermediate (intermediate vocational or higher secondary education) or higher (higher vocational education or university) education. Smoking status was classified as never smoker, ex-smoker or current smoker, and alcohol consumption as non-drinker, light drinker (0–4·9 g/d for both women and men), moderate drinker (5·0–14·9 g/d for women; 5·0–29·9 g/d for men) or heavy drinker (≥15·0 g/d for women; ≥30·0 g/d for men)[25]. Physical activity was assessed by the Cambridge Physical Activity Index score, on the basis of the frequency and total duration of activity during leisure time and work, and classified as inactive, moderately inactive, moderately active or active[26]. BMI was calculated as the ratio of measured weight to height squared (kg/m^2). Diabetes was defined as self-reported diabetes or a random glucose level ≥11·1 mmol. Hypercholesterolaemia was defined as non-fasting total cholesterol ≥6·5 mmol/l and/or the use of cholesterol-lowering medication. Hypertension was defined as systolic blood pressure ≥140 mmHg, and/or diastolic blood pressure ≥90 mmHg, and/or the use of antihypertensive medication. Low-fat dairy products were defined as milk and milk products with a fat concentration <2 g/100 g. Coffee intake was measured in cups per day and intake of nuts was measured in g/d. Intake of antioxidants comprised vitamin C, vitamin E, β-carotene, lutein, flavonoids and lignans, and was computed as described previously[27]. A standardised z score for all antioxidants was constructed at each round, on the basis of the means and standard deviations of intakes at baseline. Standardised z scores were then summed to calculate daily total intake of antioxidants. The B vitamins included B_1, B_2, B_3 and B_6, and a total vitamin B composite variable was constructed for each round (mg/d). Supplemental intakes of vitamin C, vitamin E, B complex and multi-vitamins were assessed based on questionnaire data (self-report).

Statistical analyses

Participants were categorised into tertiles (for analysis of ACR) and quartiles (for analysis of changes in eGFR) for each of the assessed foods. We used the residual method to adjust intakes of whole grains, fruit and vegetables and nutrients for total energy intake[28]. Baseline characteristics are presented according to quartiles of baseline consumption of whole grains.

To examine the prospective associations between consumption of food groups (at R2–R4) and subsequent annual changes in eGFR (between R2 and R5), the technique of generalised estimating equations (using an exchangeable correlation structure) was adopted because this method accounts for multiple observations for each participant. For these analyses, consumption of energy-adjusted food groups in R2, R3 and R4 was included as time-varying covariates (Fig. 2(a)). Linear regression coefficients and their 95% CI of changes in eGFR were calculated for continuous data (per 50 g increase) and quartiles of whole grains, fruit and vegetables, using the first quartile as the reference category.
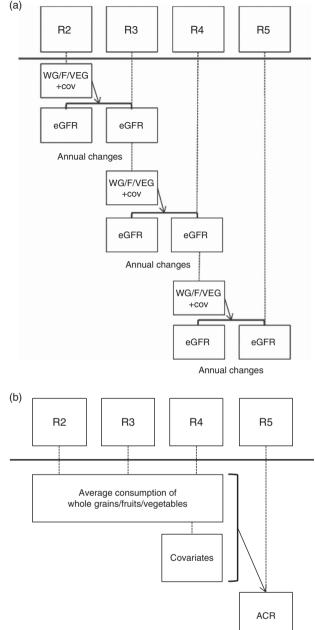
For analysis of ACR, we calculated the average consumption for each food group using 5-yearly updated information for each participant from the repeated FFQ collected at R2, R3

Fig. 2. Visualising the generalised estimating equation regression and linear regression models to study the associations between (a) consumption of whole grains (WG), fruit (F) and vegetables (VEG) (at R2–R4) and subsequent annual changes in estimated glomerular filtration rate (eGFR) (between R2 and R5), and (b) average consumption of whole grains, fruit and vegetables (at R2, R3 and R4) and albumin:creatinine ratio (ACR) (at R5).

and R4. To correct for skewness, ACR at R5 was transformed to the natural log scale. We used linear regression analysis to assess associations between tertiles of the average energy-adjusted consumption of whole grains, fruit and vegetables at R2, R3 and R4 and the natural logarithm of ACR at R5 (Fig. 2(b)). As our outcome was log-transformed, we exponentiated (back-transformed) the β-coefficients to obtain ratios of geometric means of ACR for each exposure tertile in relation to the reference category that has the null value of 1.

For both analyses, tests for trends across tertiles or quartiles were conducted by modelling the median value for each category as a continuous variable. Furthermore, we first adjusted for only age and sex (model 1). In model 2, additional adjustments were made for attained level of education and physical activity, BMI, smoking, alcohol consumption, daily energy intake, energy-adjusted intake of total protein, low-fat dairy products, coffee and nuts, supplement use and presence of diabetes, hypertension and hypercholesterolaemia. We also fitted model 3 with additional adjustment for energy-adjusted intake of Mg, fibre, vitamin B and antioxidants to investigate the possible mediating roles of these nutrients. Once participants were classified as having diabetes, hypertension or hypercholesterolaemia, they were considered to have that condition at all subsequent rounds. For analysis of changes in eGFR, all covariate variables were included as time-varying covariates. For analysis of ACR, data on covariates (other than intakes of whole grains, fruit and vegetables) collected closest to the round when ACR was measured (R4) were used. We also formally tested effect modification by adding interaction terms between the exposures and age and sex. Differences with $P < 0.05$ were considered to be statistically significant. Analyses were performed using SAS 9.4.

Results

Participant characteristics

Of 6113 participants who responded to R2, data from 3787 (62 %) were included in the analyses on changes in eGFR. There were some baseline differences between included and excluded participants, with the latter being older, less well educated and generally less healthy (online Supplementary Appendix S1). There was no difference between included and excluded participants in terms of vegetable consumption at baseline, but the consumption of total fruit and whole grains was lower among those who were excluded.

At baseline (R2), 52 % of our study population comprised women with a mean age of 45 years and an average eGFR of 104·6 ml/min per 1·73 m². Mean annual decline over 15 years of follow-up was 0·95 (sd 0·67) ml/min per 1·73 m². Furthermore, mean BMI was 25·3 kg/m², participants were physically active on average (52 %) and had a low education level (42 %). Furthermore, 27 % were current smokers and 41 % were moderate consumers of alcohol (Table 1). Compared with participants in the lowest quartile of whole-grain intake, those in the upper two quartiles were more educated, more likely to be female and had higher intakes of fruit and vegetables, low-fat dairy products, fibre, Mg, antioxidants and B vitamins; in addition, they were less likely to be current smokers and non-drinkers and more physically active.

Whole grains, fruit and vegetables and annual changes in estimated glomerular filtration rate

After adjusting for age and sex, we observed that a higher intake of whole grains was associated with a slightly less decline in eGFR per year (Table 2). Compared with the lowest quartile,

Table 1. Baseline characteristics of 3787 men and women according to quartiles of whole-grain intake
(Mean values and standard deviations: continuous values; percentages and numbers (categorical values); medians and interquartile ranges (IQR))

| | | | Quartiles of energy-adjusted whole-grain intake | | | | | | | |
| | Total study population | | <2·0 g/d (n 838) | | 2·0–23·7 g/d (n 940) | | 23·8–103·8 g/d (n 953) | | 104·0–467·5 g/d (n 1053) | |
Characteristics	Mean/%	SD/n	Mean/%	SD/n	Mean/%	SD/n	Mean/%	SD/n	Mean/%	SD/n
Age (years)	45·2	9·7	45·8	10·0	43·7	9·4	45·8	9·8	45·5	9·5
Sex (women)	52·1	1972	50·0	418	50·0	470	63·7	607	45·2	476
Education (low)	42·0	1590	54·4	456	44·3	416	39·2	374	32·5	342
Baseline eGFR (ml/min per 1·73 m²)	104·6	13·9	104·5	14·4	105·5	13·5	103·6	14·9	104·8	13·6
Dietary intake										
Energy (kJ/d)	9506	2548	6481	2531	9770	2498	8950	2619	9795	2452
Energy (kcal/d)	2272	609	2266	605	2335	597	2139	626	2341	586
Total vegetables (g/d)										
Median	114·0		107·6		110·1		118·4		118·1	
IQR	51·1		49·3		49·5		54·4		51·6	
Total fruit (g/d)										
Median	150·2		141·5		140·4		167·6		169·4	
IQR	152·8		158·6		148·3		153·6		147·8	
Coffee (cups/d)	5·0	2·6	5·4	3·0	6·2	4·2	4·8	2·4	5·0	2·5
Low-fat dairy products (g/d)	251·5	204·3	223·8	202·1	230·7	190·6	280·1	207·1	266·0	210·8
Nuts (g/d)	9·6	11·0	8·9	11·6	9·3	10·7	10·6	11·5	9·5	10·1
Total protein (g/d)	85·7	21·7	84·4	21·6	86·4	21·2	82·0	21·7	89·5	21·6
Fibre (g/d)	24·9	4·6	23·1	4·4	23·3	4·0	24·6	4·1	28·0	4·2
Mg (mg/d)	365·7	47·7	344·2	47·8	347·8	42·0	369·8	41·9	395·0	40·8
Vitamin C (mg/d)	107·9	42·5	99·4	42·1	101·6	38·2	116·3	45·2	112·5	41·9
Vitamin E (mg/d)	13·0	3·2	12·6	3·2	12·9	3·2	13·2	3·1	13·1	3·2
β-Carotene (mg/d)	1464	524	1358	527	1415	448	1543	578	1521	513
Lutein (mg/d)	1764	775	1816	817	1728	768	1764	780	1757	744
Flavonoids (mg/d)	61·7	43·2	57·2	43·6	58·4	39·9	63·1	43·4	67·0	44·8
Lignans (μg/d)	1019	253	945	245	949	228	1049	250	1114	256
Vitamin B (mg/d)	23·1	3·9	22·9	4·1	22·5	3·7	23·0	3·9	23·8	3·7
Systolic blood pressure (mmHg)	123·9	15·9	124·8	16·6	123·6	15·7	123·5	16·3	123·7	15·1
Diastolic blood pressure (mmHg)	79·3	10·6	79·5	10·5	79·3	10·9	79·5	10·5	79·0	10·6
Hypertension	28·2	1068	29·6	248	27·5	258	29·2	278	27·0	284
Total cholesterol (mmol/l)	5·4	1·0	5·5	1·0	5·3	1·0	5·5	1·0	5·4	1·0
Hypercholesterolaemia	22·1	834	24·0	201	17·3	162	242	25·4	228	21·7
Glucose (mmol/l)	5·3	1·2	5·4	1·1	5·2	1·2	5·3	1·2	5·2	1·3
Diabetes	1·2	46	1·1	9·0	1·1	10	1·0	9·0	1·7	18
BMI (kg/m²)	25·3	3·5	25·6	3·5	25·3	3·7	25·4	3·6	24·9	3·3
Overweight	39·9	1509	41·9	351	39·9	375	39·7	378	38·5	405
Smoking, current	26·9	1018	31·9	267	30·0	282	24·7	235	22·1	233
Alcohol consumption										
Non-drinker	36·2	1369	38·8	325	37·5	352	35·1	334	33·7	355
Moderate	41·1	1555	38·5	323	42·7	401	39·2	374	43·4	457
Physical activity										
Moderately active	26·8	846	25·7	178	24·3	194	27·2	214	29·7	260
Active	52·1	1645	48·8	338	54·1	433	52·3	412	52·6	460
Supplement use	10·4	395	7·5	63	11·1	104	11·7	111	11·1	117

eGFR, estimated glomerular filtration rate.

decline in eGFR, respectively, 0·10 ml/min per 1·73 m² (95 % CI 0·02, 0·17) and 0·09 ml/min per 1·73 m² (95 % CI 0·02, 0·16), per year was less in the third and fourth quartiles of whole grains, with a borderline significant trend across quartiles ($P=0·06$). However, in the model adjusted for education, dietary and lifestyle variables, only the second and third quartiles of whole grains remained significantly associated with less decline in eGFR (β 0·09; 95 % CI 0·01, 0·16 and 0·07; 95 % CI 0·002, 0·15 ml/min per 1·73 m², respectively; $P_{trend}=0·25$). Further adjustment for intake of Mg, fibre, B vitamins and antioxidants only slightly decreased this estimate, but the CI became wider and this association was further attenuated to null ($P_{trend}=0·94$).

Neither intake of fruit nor intake of vegetables (both as continuous and categorical variables) were statistically significantly associated with changes in eGFR, a pattern that did not change after adjustment for potential confounders and intermediates (Table 2).

Whole grains, fruit and vegetables and the urinary albumin: creatinine ratio

The median ACR at R5 was 9·44 mg/g (interquartile range 6·05, 16·89). There was no evidence of an association of average intakes of whole grains, fruit and vegetables at R2–R4 with ACR at R5 in any of the models (Table 3). After adjustment for all covariates in model 2, the ratio of geometric mean was 1·07 (95 % CI 0·97, 1·19), 1·05 (95 % CI 0·95, 1·16) and 1·01 (95 % CI 0·91, 1·12) in the third tertiles of, respectively, whole grains, fruit

Table 2. Associations between intake of whole grains, fruit and vegetables at rounds 2–4 and subsequent yearly changes in estimated glomerular filtration rate between rounds 2 and 5 among 3787 participants of the Doetinchem Study
(Linear regression coefficients (β) (ml/min per 1·73 m^2) and 95 % confidence intervals)

	Median intake (g/d)	Model 1*		Model 2†		Model 3‡	
		β	95 % CI	β	95 % CI	β	95 % CI
Whole grains							
Per 50 g increment		0·02	0·0004, 0·03	0·02	−0·002, 0·03	−0·005	−0·03, 0·02
Quartile 1	0·27	0	Ref.	0	Ref.	0	Ref.
Quartile 2	4·79	0·06	−0·02, 0·13	0·05	−0·03, 0·13	0·04	−0·04, 0·12
Quartile 3	65·2	0·10	0·02, 0·17	0·09	0·01, 0·16	0·06	−0·02, 0·14
Quartile 4	139·0	0·09	0·02, 0·16	0·07	0·002, 0·15	0·01	−0·08, 0·09
$P_{\text{for trend}}$		0·06		0·25		0·94	
Fruit							
Per 50 g increment		0·006	−0·003, 0·01	0·009	−0·001, 0·02	0·01	−0·003, 0·02
Quartile 1	54·0	0	Ref.	0	Ref.	0	Ref.
Quartile 2	125·1	−0·01	−0·09, 0·06	−0·01	−0·09, 0·06	−0·02	−0·09, 0·06
Quartile 3	199·5	−0·02	−0·09, 0·05	−0·02	−0·09, 0·05	−0·03	−0·10, 0·05
Quartile 4	330·1	0·02	−0·04, 0·09	0·04	−0·03, 0·11	0·03	−0·06, 0·11
$P_{\text{for trend}}$		0·42		0·22		0·46	
Vegetables							
Per 50 g increment		0·005	−0·03, 0·04	−0·003	−0·03, 0·03	0·003	−0·04, 0·04
Quartile 1	72·7	0	Ref.	0	Ref.	0	Ref.
Quartile 2	101·8	0·03	−0·04, 0·10	−0·004	−0·08, 0·07	0·0006	−0·08, 0·08
Quartile 3	126·7	0·06	−0·02, 0·13	0·05	−0·03, 0·12	0·05	−0·03, 0·13
Quartile 4	168·7	0·05	−0·02, 0·12	−0·004	−0·08, 0·07	0·01	−0·08, 0·11
$P_{\text{for trend}}$		0·54		0·85		0·61	

Ref., referent values.
* Model 1: adjusted for age at baseline and sex.
† Model 2: model 1 and highest attained level of education and time-dependent physical activity, BMI, smoking, alcohol consumption, daily energy intake (kJ (kcal)), energy-adjusted intake of total protein, low-fat dairy products, coffee and nuts, supplement use, presence of diabetes, hypertension and hypercholesterolaemia.
‡ Model 3: model 2 and energy-adjusted intake of Mg, fibre, vitamin B and antioxidants.

Table 3. Associations between average intake of whole grains, fruit and vegetables at rounds 2–4 and albumin:creatinine ratio (ACR) at round 5 among 1903 participants of the Doetinchem Study*
(Geometric means (exponentiated linear regression coefficients) and 95 % confidence intervals)

	Model 1†		Model 2‡		Model 3§	
	Mean	95 % CI	Mean	95 % CI	Mean	95 % CI
Whole grains						
Tertile 1	1	Ref.	1	Ref.	1	Ref.
Tertile 2	1·06	0·93, 1·13	1·05	0·95, 1·15	1·05	0·95, 1·16
Tertile 3	1·02	0·93, 1·13	1·07	0·97, 1·19	1·07	0·96, 1·20
$P_{\text{for trend}}$	0·61		0·14		0·23	
Fruit						
Tertile 1	1	Ref.	1	Ref.	1	Ref.
Tertile 2	1·04	0·94, 1·15	1·06	0·96, 1·17	1·04	0·94, 1·15
Tertile 3	1·01	0·91, 1·12	1·05	0·95, 1·16	1·01	0·90, 1·13
$P_{\text{for trend}}$	0·83		0·31		0·89	
Vegetables						
Tertile 1	1	Ref.	1	Ref.	1	Ref.
Tertile 2	1·00	0·90, 1·11	1·01	0·91, 1·11	0·98	0·90, 1·08
Tertile 3	0·99	0·90, 1·09	1·01	0·91, 1·12	0·97	0·86, 1·08
$P_{\text{for trend}}$	0·82		0·85		0·54	

Ref., referent values.
* Rows include ratios of geometric means of ACR at R5 obtained by back-transforming coefficients as the outcome was log-transformed in analyses. These are interpreted as percentage (relative) differences; for example, the results from model 3 for whole grains show a non-significant 7 % increase in those with the highest tertile of intake compared with those in the lowest tertile.
† Model 1: adjusted for age at baseline and sex.
‡ Model 2: model 1 and highest attained level of education and time-dependent physical activity, BMI, smoking, alcohol consumption, daily energy intake (kJ (kcal)), energy-adjusted intake of total protein, low-fat dairy products, coffee and nuts, supplement use, presence of diabetes, hypertension and hypercholesterolaemia.
§ Model 3: model 2 and energy-adjusted intake of Mg, fibre, vitamin B and antioxidants.

and vegetables. Adjustment for intake of Mg, fibre, B vitamins and antioxidants had little effect on these estimates.

Finally, in both analyses, there were no statistical significant interactions between age or sex and studied food groups.

Discussion

In this analysis in a large cohort of generally healthy men and women, we found a trend towards slightly less decline in renal

function among those with higher intakes of whole grains. This trend, however, was attenuated and no longer significant in multivariate models. Intakes of fruit and vegetables were both not associated with changes in renal function. Furthermore, no associations were observed with continuous urinary ACR.

Earlier findings from the prospective FHS, NOMAS and the Nurses' Health Study that showed that higher diet quality[16,29], better adherence to a Mediterranean Diet[15] or a DASH-style diet, but not prudent diet[30], was associated with reduced incidence of low eGFR or risk of rapid decline. As whole grains, fruit and vegetables are highly presented in these dietary patterns, it is expected that these individual foods are associated with renal function too. In our study, this was not the case. Until now, few studies have examined the effects of consumption of whole grains, fruit and vegetables on renal function. Similar to our findings, the FHS did not find associations of consumption of whole grains, fruit and vegetables with odds of micro-albuminuria, incident low eGFR or rapid eGFR decline[29]. However, a high vegetable intake was found to be associated with a significantly lower risk of incident eGFR <60 ml/min per 1·73 m^2 among participants of the NOMAS study[15]. In addition, cross-sectional findings from the MESA study showed that higher intakes of whole grains and fruit, but not vegetables, were associated with lower ACR[10]. Differences in findings may be because of differences in cohort composition and study design. For example, participants of the NOMAS and MESA study included elderly people of mixed origin with relatively low eGFR at baseline, whereas participants of the Doetinchem Study were relatively young, white people with well-preserved renal function. Furthermore, creatinine-based eGFR was used in the NOMAS study, which is known to be less accurate in comparison with creatinine- and cystatin C-based estimates of GFR[24]. In addition, FFQ used and categorisation of food groups in NOMAS and MESA differed from ours, and both studies lacked repeated dietary assessments over time. Relative validity of FFQ to estimate intakes of food groups in NOMAS and MESA, however, may be higher than in our study population, but this information is not provided in their reports, making it difficult to examine this potential difference. Furthermore, only the MESA study reported the average intakes of food groups. Although it is difficult to make direct comparisons of dietary intake between countries, intakes in our cohort seemed to be similar (fruit) or slightly higher (vegetables and whole grains). Still, it may not have been high enough to detect an impact on eGFR changes and ACR in a relatively healthy cohort. On the other hand, results from our group have shown that higher intakes of whole grains, fruit and vegetables are associated with decreased risk of chronic obstructive pulmonary disease and CHD in the Doetinchem Study[20,31]. These findings indicate that, although self-reported, the selected food groups do relate to other outcomes in previous studies. Nevertheless, additional large prospective population-based studies, with objective measurement of individual foods and food groups in addition to accurate estimates of renal function, are needed to investigate whether our findings can be confirmed.

The relatively narrow CI in our study suggest that we had sufficient power to assess the association between diet and renal outcomes. Furthermore, compared with the previous investigations, our observational study has the advantage of 15 years of follow-up and inclusion of over 3500 men and women of the general population. Of the studies on eGFR changes, ours is the largest to date to examine the association between consumption of whole grains, fruit and vegetables and renal function outcomes. Repeated measurements of exposures and outcomes enabled us to take into account changes over time. In addition, the use of both creatinine and cystatin C in estimating the GFR currently provides the most precise and accurate estimate of kidney function[24]. Because all available samples for each participant were measured in one assay run, we optimally reduced the chances of interassay variation[23].

There are a few limitations. First, the participants not included in our analyses were generally less healthy than included participants, which means we cannot exclude some selection bias. Second, intakes of exposures were based on self-report, which may have introduced some errors. However, the FFQ was previously validated and was found to be useful for the assessment of usual intake[21]. Energy-adjusted correlation coefficients for fruit and bread were reasonable to good, with correlation coefficients >0·56. For vegetable intake, the relative validity was lower, suggesting that these particular findings should be interpreted with caution. Third, although exposure data were measured before ACR measurements were taken, ACR was measured only once in R5 in 2008–2011. We therefore do not know whether participants had an altered ACR before 2008 and whether they changed their diet because of it. Fourth, the number of participants with unstable intakes of whole grains, fruit and vegetables was too low to perform stratified analysis of stable v. unstable intakes. Fifth, there may be some residual confounding because we did not collect information on salt intake and drug subclasses. Finally, the low risk of renal dysfunction in our study population meant that the number of persons with microalbuminuria was too low for a meaningful analysis; instead, we modelled urinary ACR continuously.

In conclusion, consumption of whole grains, fruit and v egetables is not associated with changes in eGFR and mean ACR in young to middle-aged adults from a population-based cohort. This is contrary to expectations, given that previous studies have shown associations between a higher diet quality or better adherence to a Mediterranean diet and reduced incidence of low eGFR or risk of rapid decline. Further research is needed to replicate our findings in other large prospective population-based studies and to determine which specific food groups are responsible for the associations found with the Mediterranean diet.

All authors were involved in the interpretation of the data, critically reviewed the manuscript and approved the final version. G.-C. M. H.-G. and A. M. W. S. were responsible for the manuscript's contents.

None of the authors declared a conflict of interest.

Supplementary material

For supplementary material/s referred to in this article, please visit https://doi.org/10.1017/S0007114517001726

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