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ORIGINAL ARTICLE

Nutrient-rich foods, cardiovascular diseases and all-cause mortality: the Rotterdam study

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BACKGROUND/OBJECTIVES: The nutrient-rich food (NRF) index assesses nutrient quality of individual food items by ranking them according to their nutrient composition. The index reflects the nutrient density of the overall diet. We examined the associations between the NRF9.3 index—a score on the basis of nine beneficial nutrients (protein, fiber, vitamins and minerals) and three nutrients to limit (saturated fat, sugar and sodium)—incidence of cardiovascular disease (CVD) events and all-cause mortality.
SUBJECTS/METHODS: A total of 4969 persons aged 55 and older from the Rotterdam Study, a prospective cohort study in the Netherlands, were studied. First, all foods were scored on the basis of their nutrient composition, resulting in an NRF9.3 score on food item level. Subsequently, they were converted into individual weighted scores on the basis of the amount of calories of each food item consumed by the subjects and the total energy intake. The hazard ratios (HRs) of the NRF9.3 index score were adjusted for age, gender, body mass index, smoking history, doctor-prescribed diet, alcohol consumption and education.
RESULTS: Food groups that contributed most to the NRF9.3 index score were vegetables, milk and milk products, fruit, bread and potatoes. A high NRF9.3 index score was inversely associated with all-cause mortality (HR Q4 versus Q1: 0.84 (95% confidence interval: 0.74, 0.96)). Associations were stronger in women than in men. The NRF9.3 index score was not associated with incidence of CVD.
CONCLUSION: Elderly with a higher NRF9.3 index score, indicating more beneficial components and/or less limiting components, had a lower risk of all-cause mortality. Consuming a nutrient-dense diet may improve survival.

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INTRODUCTION

The Dietary Guidelines for Americans, 2010 recommend eating foods that are low in calories and to focus on consuming more nutrient-dense foods and beverages.[1] Diet quality scores, for example the Healthy Eating Index (HEI-2005),[2,3] generally assess how closely dietary patterns align with national dietary guidelines and how diverse the variety of healthy choices is within predetermined core food groups. They can be used retrospectively to analyze the diet quality of populations and to monitor their changes over time. Furthermore, they can be used to examine relationships with health outcomes. Several studies have reported an inverse association between diet quality scores and mortality.[4–10]

A key element of diet quality is nutrient adequacy. Traditionally, the nutrient adequacy of a diet was on the basis of the comparison of nutrient intakes with the recommended daily allowances. Various nutrient quality models, such as the nutrient-rich food (NRF) index,[11] have been developed to evaluate the nutrient quality of individual foods by ranking them on the basis of their nutrient composition. A science-based definition of nutrient density or nutrient-dense foods does not yet exist, but all nutrient quality models aim to measure the nutrient density of the overall diets of individuals and populations.[12] The NRF index has two components: (1) the nutrient-rich (NR) component which is on the basis of a variable number of beneficial nutrients (including protein, dietary fiber and a number of vitamins and minerals) and (2) the limiting nutrients (LIM) component which is on the basis of saturated fat, added or total sugar and sodium. In the simplest algorithm, the LIM index is subtracted from the NR index. Fulgoni *et al.*[13] compared various NRF indexes against the HEI-2005 in the National Health and Nutrition Examination Survey and the best results were obtained for the NRF9.3 index composed of a positive sub-score on the basis of: protein; dietary fiber; vitamins A, C and E; calcium; iron; potassium; and magnesium, and the negative sub-score on the basis of saturated fat, added sugar and sodium. These nutrients were selected because they are underrepresented or overconsumed in the American diet and subpopulations,[11] but are also believed to be of public health relevance in other Western populations.

Although the NRF9.3 index score has been proposed to predict overall diet quality, it has not yet been evaluated with respect to health outcomes. Therefore, we examined the association between the NRF9.3 index, major cardiovascular disease (CVD) events and all-cause mortality in the Rotterdam Study, a community-based cohort study. We hypothesize subjects with a higher index score to have a lower risk of all-cause mortality and CVD.

MATERIALS AND METHODS

Study design and population

The present study was carried out as part of the Rotterdam Study, a prospective cohort study among 7983 elderly persons who live in one defined geographic area in Rotterdam, The Netherlands. The rationale and design of the study have been described previously.[14] The Rotterdam Study focusses on the incidence and determinants of major chronic

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diseases in elderly, including neurogeriatric diseases, CVD, locomotor diseases and ophthalmologic diseases. All inhabitants of the Rotterdam district Ommoord, aged 55 years and over, were invited to participate. The Rotterdam Study has been approved by the Medical Ethics Committee and all participants provided written informed consent. The baseline examinations started in August 1990 and continued until June 1993. The subjects were visited at home by trained interviewers to collect data on current health and medical history, medication use, lifestyle, social and economic status, housing and living condition, mental status and mobility. The subjects subsequently visited the research center twice for baseline clinical examinations and dietary assessment. Dietary data were available for 5435 subjects.[15,16] Subjects with missing baseline data on health risk indicators and other covariates ($n = 466$) were excluded from the analysis. Complete data were available for 4969 subjects. Subjects with prevalent CVD ($n = 1340$) were excluded from the analyses of major CVD events because they had been at increased CVD risk and had changed their diet as a result of their disease, which might distort the association between diet and CVD. Prevalent CVD included coronary heart disease and stroke and was ascertained with a standardized questionnaire on medical history during a baseline home interview, confirmed by ECG at the research center, or additional clinical information including access to the Nationwide Medical Registry and full screening of GP's records.[17] Thus, the subjects entered into the analyses of major CVD events were 3629 men and women.

Dietary assessment

At baseline, a two-step dietary assessment was conducted, consisting of a simple self-administered questionnaire followed by a structured interview with a trained dietician.[18] Participants completed a meal-based checklist at home, on which they indicated all foods and drinks that they had consumed at least twice a month during the preceding year. Subsequently, a trained dietitian interviewed the participants at the research center. An extensive, validated, semi-quantitative food-frequency questionnaire was used to quantify the amounts and frequencies of food items that had been noted by participants as consumed frequently in the checklist. For each item, the frequency was recorded in times per day, week or month. In addition, consistency checks of the completed dietary questionnaire were performed and questions were asked about dietary habits, the use of supplements and doctor-prescribed diets, such as a diabetes diet, a diet restricted in sodium, fat, cholesterol, energy, fiber, lactose, gluten or calcium, or a diet enriched with protein or fiber. Subsequently, the average daily intake of all food items and food groups was estimated for each person. Foods were converted to energy and nutrient intake with a computerized version of the Dutch food composition table from 1993.[19] To estimate dietary fiber intake, the Dutch food composition table from 1996 was used.[20] The Dutch food composition database contains data on the nutritional composition of all food products and dishes consumed regularly by a large proportion of the Dutch population. The amounts of nutrients given in the table are the total amounts including both naturally occurring and added micronutrients.

Calculation of the NRF index scores

In the present study, the NRF9.3 index as proposed by Fulgoni[13] was used to derive dietary patterns as this score explained most of the variation in the HEI-2005 compared with other NRF algorithms. First, we scored all foods consumed by each subject using the NRF9.3 algorithms (Table 1). This resulted in a NRF9.3 score (per 100 kcal) for every food item, that is, an NRF9.3 food score. We used the recommended daily allowances as set by the European Union[21] and the labeling reference intake values as set by the European Food Safety Authority as reference daily values (DVs)[21–25] (Table 2). The percentage of reference DV for each nutrient was capped at 100% DV to avoid overvaluing of food items that provide very large amounts of a single nutrient.[11] Table 3 shows the mean NRF index scores per food group; the scores were on the basis of 253 food items from 20 food groups. Vegetables had the highest scores, whereas sugar, confectionary and sweets had the lowest. Second, the NRF9.3 food scores per food item were converted to individual NRF9.3 index scores by multiplying the amount of kcal consumed of each food item, in 100-kcal units, by the NRF9.3 food scores and then summing these scores for each subject. Next, the NRF9.3 index scores were divided by the number of 100-kcal units of the subjects' total energy intake to provide a 'weighted average' diet quality score. Higher NRF9.3 index scores indicate higher nutrient density per 100 kcal and thus, subjects with a high NRF9.3 index score were considered to have a healthier dietary pattern than those with a low NRF9.3 index score. Because only limited data on added sugar intake were available, total sugar intake was used instead.

Covariate assessment

Height was measured in centimeters while the subject stood upright without shoes, with heels together and head in the Frankfurt plane. Weight was measured in 0.1-kg increments while the subject stood upright without shoes and heavy clothing and the body mass index (BMI) was calculated (kg/m^2). Smoking history was assessed during the home interview, and subjects were categorized into never, former and current smokers. Alcohol consumption was assessed with the semi-quantitative food-frequency questionnaire. Subjects' intake of alcohol was categorized into no intake, moderate intake ($\leqslant$20 g/day for men and $\leqslant$10 g/day for women), and high intake (>20 g/day for men and >10 g/day for women). Level of education was categorized into three groups: primary; intermediate general and lower vocational; higher education and university.[15]

Table 2. Recommended and maximum daily values for selected nutrients

Nutrient	*Recommended daily value*[a]	*Maximum daily value*[a]
Nutrient-rich (NR) components		
Protein (g)	57 (ref. 22)	
Dietary fiber (g)	25 (ref. 24)	
Vitamin A (μgRE)	800 (ref. 21)	
Vitamin E (mg)	12 (ref. 21)	
Vitamin C (mg)	80 (ref. 21)	
Calcium (mg)	800 (ref. 21)	
Magnesium (mg)	375 (ref. 21)	
Iron (mg)	14 (ref. 21)	
Potassium (mg)	2000 (ref. 21)	
Nutrients to limit (LIM)		
Saturated fat (g)		20 (ref. 23)
Sugar (g)		
Total		90 (ref. 23)
Added		45 (ref. 23)
Sodium (mg)		2400 (ref. 23)

[a]Based on an intake of 2000 kcal per day.

Table 1. Nutrient-rich foods (NRFs) algorithms[11]

Model	*Algorithm*	*Comment*
$NR9_{100\ kcal}$[a]	$\sum_{i=1-9}(Nutrient_i/RDV_i)*100$	$Nutrient_i$: content of nutrient i in 100-kcal edible portion; RDV_i: recommended daily values for nutrient i
$LIM3_{100\ kcal}$[b]	$\sum_{i=1-3}(Nutrient_i/MDV_i)*100$	$Nutrient_i$: content of limiting nutrient i in 100-kcal edible portion; MDV_i: maximum xdaily values for nutrient i
$NRF9.3_{100\ kcal}$	NR9-LIM3	Difference between sums

[a]NR: nutrient-rich score, consisting of nine beneficial nutrients: protein, dietary fiber, vitamin A, vitamin C, vitamin E, calcium, magnesium, iron and potassium.
[b]LIM: limited nutrient score, consisting of three nutrients to limit: saturated fat, total or added sugar and sodium.

Table 3. Mean nutrient-rich food index scores per 100 kcal on food item level

Food groups (no. of food items included)	*Mean index scores on food item level*		
	NR9	*LIM3*	*NRF9.3*
Potatoes (1)	81.4	1.7	79.7
Alcoholic and non-alcoholic beverages (16)	97.5	24.5	73.0
Bread (8)	35.1	11.8	23.3
Eggs (1)	56.7	15.1	41.6
Fruit (15)	108.6	24.0	84.6
Pastry, cake and biscuits (6)	17.5	19.1	− 1.6[a]
Cereal products and binding agents (7)	81.7	4.7	77.0
Vegetables (34)	350.8	20.7	330.1
Savory sandwich filling (1)	50.1	8.4	41.7
Cheese (7)	68.1	33.0	35.1
Milk and milk products (33)	54.2	24.8	29.5
Soy and vegetarian products (2)	79.7	10.3	69.4
Nuts, seeds and snacks (8)	36.6	12.6	24.0
Legumes (2)	95.4	1.3	94.2
Mixed dishes (4)	32.4	11.6	20.8
Soups (2)	110.0	41.3	68.8
Sugar, confectionary, sweets (15)	15.9	23.7	− 7.8[a]
Fats, oils and savory sauces (28)	29.6	19.5	10.1
Fish (17)	67.5	17.3	50.2
Meat, meat products and poultry (46)	54.6	20.8	33.8

Abbreviations: LIM, limiting nutrient; NR, nutrient rich; NRF, nutrient-rich food. [a]Negative contribution to scores might occur when a food item contributes more to LIM3 than to NR9.

A trained research assistant measured sitting systolic and diastolic blood pressure twice with a random-zero sphygmomanometer after a 5-min rest; values were averaged. Hypertension was defined as a systolic blood pressure ⩾160 mm Hg or diastolic blood pressure ⩾95 mm Hg or use of antihypertensive medication according to the guidelines of the World Health Organization and International Society of Hypertension.[26] Diabetes mellitus was considered present when the subject reported antidiabetic treatment, or when random or post-load plasma glucose levels were ⩾11.1 mmol/l. Data on physical activity were collected during the third phase of the Rotterdam Study (1997–2000) by means of a validated questionnaire and were only available in ~70% ($n = 3593$) of the subjects included in the present study.[27]

Case ascertainment

Mortality data were assessed until 1 January 2008 and major CVD events until 1 January 2007 through continuous monitoring of the municipal address files and computerized reports from general practitioners on the deaths or the occurrence of CVD events of the subjects.[14,28] The composite endpoint incident CVD included all of the first events attributed to coronary heart disease or ischemic stroke. For the diagnosis of cardiac events, two research physicians independently coded all recorded events. In case of disagreement, a decision was made by a medical expert in the field. In case of stroke, events were coded by two research physicians and an experienced neurologist. All of the events were coded according to the International Classification of Diseases, 10th Edition. Coronary heart disease was defined as the occurrence of a nonfatal myocardial infarction (ICD-10 code I21), a percutaneous transluminal coronary angioplasty, a coronary artery bypass graft, other forms of acute (I24) or chronic ischemic heart disease (I25), and mortality attributed to coronary artery disease (I20, I21, I24, I25, I46 and R96). Ischemic stroke was defined as incident fatal and nonfatal ischemic stroke (I63).

Statistical analysis

The subjects were divided into quartiles on the basis of the individual NRF9.3, NR9 and LIM3 index scores. The baseline characteristics of the subjects were compared between quartiles of the NRF9.3 index score using analysis of variance for continuous variables and the X^2 statistic for categorical variables. Cox proportional hazard models were used to examine the association between the index scores and all-cause mortality. Hazard ratios (HRs) were calculated separately for men and women, using the lowest quartile of the score as reference. The HRs were adjusted for age and sex (model 1), and additionally for BMI, smoking history, prescribed diet, alcohol consumption and education level (model 2). To perform a test for linear trend across the quartiles, the median value of each quartile was entered into the models. Sensitivity analyses were performed to assess the robustness of the results. All statistical analyses were carried out using SAS (version 9.2). Two-sided *P*-values below 0.05 were considered statistically significant.

RESULTS

Population characteristics

Persons in the highest quartile of the NRF9.3 index score were more likely to be female, younger and had higher BMI and physical activity levels than those in the lowest quartile (Table 4). Furthermore, persons with a higher NRF9.3 index score were also more likely to have diabetes, hypertension and to be on a doctor-prescribed diet. Mean NRF9.3 index score was higher in women (mean ± standard deviation: 35.8 ± 9.6) than in men (mean ± standard deviation: 30.6 ± 8.2).

Energy density of the diet was lower among subjects in the highest quartile of the NRF9.3 index score than lowest quartile (Table 4). Persons in the highest quartile of the NRF9.3 index score consumed less bread, potatoes, pastry, fats and oils, sugar and sweets, and meat, but consumed more vegetables (including legumes), fish and milk products as compared with those in the lowest quartile (Table 5). Main contributors of the NRF9.3 index score were vegetables, milk and milk products, fruit, bread and potatoes.

NRF9.3 index scores, all-cause mortality and major CVD incidence

During 63 734 person-years of follow-up up to 1 January 2008, 1047 men and 1110 women died. Follow-up for major CVD was 56 389 person-years up to 1 January 2007, in which 611 men and 505 women experienced coronary heart disease or ischemic stroke, of which 319 men and 322 women without prevalent CVD at baseline. A higher NR9 index score was associated with a lower risk of mortality; the multiple adjusted HR in the 4th quartile (Q4) versus the 1st quartile (Q1) was 0.84 (95% confidence interval (CI) = 0.74, 0.96). A higher LIM3 index score was associated with a higher all-cause mortality risk with an HR in Q4 versus Q1 of 1.17 (95% CI = 1.03, 1.34) after adjustment (Table 6). Correspondingly, a higher NRF9.3 index score was associated with a lower mortality risk (HR in Q4 versus Q1 = 0.84, 95% CI = 0.74, 0.96).

Associations of the index score were weaker for incident CVD and were not significant; the HR for the NRF9.3 index score in Q4 versus Q1 was 0.93 (95% CI = 0.73, 1.18) (Table 7). This was mainly due to the absence of an association between the NR9 and CVD, whereas for the LIM3 index score, the HRs were of similar magnitude as for all-cause mortality. The associations between the NR9 and NRF9.3 score were stronger for fatal major CVD events (210 cases) than for nonfatal major CVD events (431 cases), but not statistically significant. The LIM3 index score was positively related to CVD mortality. The HR in Q4 versus Q1 was 2.05 (95% CI = 1.32, 3.19).

Interaction for gender was significant for total mortality (*P*-value for interaction < 0.05), but not for major CVD events. The HR for all-cause mortality in Q4 versus Q1 of the NRF9.3 index was 0.75 (95% CI = 0.63, 0.89) in women and 0.91 (95% CI = 0.76, 1.09) in men after multiple adjustments. The associations between the NRF9.3 index score and major CVD including persons with prevalent CVD ($n = 4969$) in the analyses were similar: HR in Q4 versus Q1 was 0.90 (95%CI = 0.75, 1.07).

Data on added sugar were not available for ~10% of food items consumed. As far as we could investigate these data, replacing total sugar with added sugar in the index scores did not change

Table 4. Baseline characteristics[a] of 4969 men and women from the Rotterdam Study according to quartiles of the nutrient-rich food 9.3 (NRF9.3) index score

Characteristic	*Q1*	*Q2*	*Q3*	*Q4*	P-*trend*
NRF9.3 index score	22.4 ± 4.0	30.3 ± 1.6	36.1 ± 1.8	45.7 ± 6.5	< 0.0001
NR9 index score	41.9 ± 4.0	49.1 ± 2.5	54.5 ± 2.5	63.8 ± 6.8	< 0.0001
LIM3 index score	19.5 ± 2.1	18.7 ± 2.0	18.4 ± 1.7	18.1 ± 1.8	< 0.0001
Age, years	69 ± 8	68 ± 8	67 ± 7	67 ± 8	< 0.0001
Male gender	723 (58)	573 (46)	468 (38)	280 (23)	< 0.0001
Body mass index, kg/m^2	25.7 ± 3.5	26.1 ± 3.4	26.5 ± 3.5	27.0 ± 3.8	< 0.0001
Smoking history					< 0.0001
Current	407 (33)	298 (24)	232 (19)	216 (17)	
Former	540 (43)	530 (43)	568 (46)	504 (41)	
Never	295 (24)	414 (33)	443 (36)	522 (42)	
Energy density, kcal/g	0.8 ± 0.2	0.7 ± 0.1	0.7 ± 0.1	0.6 ± 0.1	< 0.0001
Doctor-prescribed diet	83 (7)	129 (10)	174 (14)	278 (22)	< 0.0001
Alcohol use					< 0.0001
No	236 (19)	219 (18)	261 (21)	299 (24)	
Moderate	599 (48)	654 (53)	668 (54)	691 (56)	
High	407 (33)	369 (30)	314 (25)	252 (20)	
Education level					0.12
Primary school	445 (36)	421 (34)	397 (32)	440 (35)	
Lower general and vocational	332 (27)	346 (28)	388 (31)	366 (29)	
Higher and university	465 (37)	475 (38)	458 (37)	436 (35)	
Physical activity, kcal/day[b]	814 ± 495	897 ± 536	911 ± 538	954 ± 533	< 0.0001
Diabetes mellitus	96 (8)	106 (9)	129 (10)	129 (10)	0.05
Hypertension	367 (30)	406 (33)	426 (34)	464 (37)	0.001

Abbreviations: LIM, limiting nutrient; NR, nutrient rich; Q1, 1st quartile; Q2, 2nd quartile; Q3, 3rd quartile; Q4, 4th quartile. [a]Mean ± s.d. and number (percentage). [b]Data on physical activity was only available for 3593 subjects.

Table 5. Average daily food group intakes (mean ± s.d.) from 4969 subjects of the Rotterdam Study according to quartiles of the nutrient-rich food 9.3 (NRF9.3) index score and mean contribution of food groups to index scores

Food group	*Food group intake (g)*				P-*value*	*Mean contribution (%) to score*[a]		
	Q1	*Q2*	*Q3*	*Q4*		*NR9*	*LIM3*	*NRF9.3*
Potatoes	132 ± 67	132 ± 70	134 ± 71	119 ± 67	< 0.0001	8	0	13
Alcoholic and non-alcoholic beverages	1323 ± 493	1334 ± 450	1340 ± 506	1435 ± 534	< 0.0001	4	3	4
Bread	145 ± 58	142 ± 55	136 ± 52	119 ± 47	< 0.0001	12	10	13
Eggs	14 ± 9	13 ± 8	13 ± 8	12 ± 8	< 0.0001	1	1	1
Fruit	171 ± 108	218 ± 121	249 ± 118	199 ± 152	< 0.0001	12	9	14
Pastry, cake, and biscuits	45 ± 40	43 ± 31	37 ± 25	29 ± 21	< 0.0001	3	8	− 1
Cereal products and binding agents	13 ± 22	17 ± 32	19 ± 23	23 ± 31	< 0.0001	1	0	1
Vegetables	171 ± 71	199 ± 72	213 ± 80	263 ± 172	< 0.0001	12	2	18
Savory sandwich filling	1.3 ± 4.3	1.5 ± 4.7	1.8 ± 5.2	1.4 ± 5.1	0.21	0	0	1
Cheese	36 ± 28	38 ± 24	37 ± 21	35 ± 19	0.37	7	12	5
Milk and milk products	344 ± 249	374 ± 239	420 ± 257	454 ± 282	< 0.0001	14	14	15
Soy and vegetarian products	0.2 ± 2.4	0.3 ± 3.2	0.7 ± 5.5	1.5 ± 8.9	< 0.0001	0	0	0
Nuts, seeds and snacks	9 ± 17	7 ± 13	7 ± 12	4 ± 9	< 0.0001	0	1	2
Legumes	1.3 ± 5.4	1.8 ± 6.4	2.2 ± 7.3	3.1 ± 16.7	< 0.0001	1	0	0
Mixed dishes	10 ± 17	10 ± 19	9 ± 15	7 ± 12	< 0.0001	0	0	0
Soups	62 ± 67	60 ± 70	57 ± 62	59 ± 71	0.16	0	3	1
Sugar, confectionary, sweets	68 ± 43	41 ± 29	29 ± 22	17 ± 17	< 0.0001	2	10	− 5
Fats, oils and savory sauces	46 ± 19	42 ± 19	39 ± 19	32 ± 17	< 0.0001	10	13	7
Fish	14 ± 18	15 ± 18	15 ± 18	19 ± 20	< 0.0001	1	1	2
Meat, meat products and poultry	117 ± 51	113 ± 51	108 ± 46	96 ± 44	< 0.0001	9	13	7

Abbreviations: LIM, limiting nutrient; NR, nutrient rich; Q1, 1st quartile; Q2, 2nd quartile; Q3, 3rd quartile; Q4, 4th quartile. [a]Negative contribution to scores might occur when a food item contributes more to LIM3 than to NR9.

the strength of the associations. Furthermore, excluding 664 persons, women with a doctor-prescribed diet from the analyses changed our results only slightly: HR for Q4 versus Q1 of the NRF9.3 index score was 0.80 (95% CI = 0.69, 0.92) for all-cause mortality and 0.86 (95% CI = 0.71, 1.05) for incident CVD. Additional adjustment for physical activity level among those with data available ($n = 3293$) attenuated the associations: HR for NRF9.3 index score Q4 versus Q1 was 0.90 (95% CI = 0.69, 0.92) for

Table 6. The association between the nutrient-rich food 9.3 index scores and all-cause mortality in 4969 men and women in the Rotterdam Study

	No. of events	Model 1[a]		Model 2[b]	
		HR	95% CI	HR	95% CI
NR9 index score					
Q1	633	1	(ref)	1	(ref)
Q2	540	0.86	0.77, 0.97	0.90	0.80, 1.01
Q3	532	0.86	0.76, 0.96	0.89	0.79, 1.00
Q4	452	0.81	0.72, 0.92	0.84	0.74, 0.96
P-trend		0.001		0.01	
LIM3 index score					
Q1	497	1	(ref)	1	(ref)
Q2	494	1.00	0.88, 1.13	1.07	0.94, 1.21
Q3	549	1.06	0.94, 1.20	1.14	1.00, 1.29
Q4	617	1.12	0.99, 1.27	1.17	1.03, 1.34
P-trend		0.03		0.02	
NRF9.3 index score					
Q1	645	1	(ref)	1	(ref)
Q2	541	0.86	0.76, 0.96	0.89	0.79, 1.00
Q3	522	0.84	0.75, 0.95	0.88	0.78, 0.99
Q4	449	0.81	0.72, 0.92	0.84	0.74, 0.96
P-trend		0.001		0.01	

Abbreviations: CI, confidence interval; HR, hazard ratio; LIM, limited nutrient; NR, nutrient rich; NRF, nutrient-rich food; Q1, 1st quartile; Q2, 2nd quartile; Q3, 3rd quartile; Q4, 4th quartile. [a]Adjusted for age (years) and gender. [b]Adjusted for age (years), gender, body mass index (kg/m^2), smoking history (current, former, never), doctor-prescribed diet (yes, no), alcohol consumption (no, moderate, high) and education level (low, intermediate, high).

Table 7. The association between the nutrient-rich food 9.3 index scores and major cardiovascular disease incidence in 3629 men and women in the Rotterdam Study

	No. of events	Model 1[a]		Model 2[b]	
		HR	95% CI	HR	95% CI
NR9 index score					
Q1	172	1	(ref)	1	(ref)
Q2	168	1.06	0.86, 1.32	1.06	0.86, 1.32
Q3	155	1.03	0.83, 1.28	1.01	0.81, 1.27
Q4	146	1.09	0.86, 1.38	1.03	0.81, 1.32
P-trend		0.53		0.91	
LIM3 index score					
Q1	161	1	(ref)	1	(ref)
Q2	151	1.00	0.80. 1.25	1.05	0.83, 1.32
Q3	167	1.12	0.90. 1.39	1.19	0.94, 1.50
Q4	162	1.08	0.86. 1.35	1.15	0.90, 1.47
P-trend		0.40		0.23	
NRF9.3 index score					
Q1	182	1	(ref)	1	(ref)
Q2	160	0.93	0.75. 1.15	0.92	0.74, 1.14
Q3	154	0.93	0.75. 1.16	0.91	0.73, 1.13
Q4	145	0.99	0.79, 1.25	0.93	0.73, 1.18
P-trend		0.93		0.55	

Abbreviations: CI, confidence interval; HR, hazard ratio; LIM, limited nutrient; NR, nutrient rich; NRF, nutrient-rich food; Q1, 1st quartile; Q2, 2nd quartile; Q3, 3rd quartile; Q4, 4th quartile. [a]Adjusted for age (years) and gender. [b]Adjusted for age (years), gender, body mass index (kg/m^2), smoking history (current, former, never), doctor-prescribed diet (yes, no), alcohol consumption (no, moderate, high) and education level (low, intermediate, high).

mortality and 0.90 (95% CI = 0.68, 1.18) for CVD. Excluding persons in the top and bottom 5% of the ratio of energy intake to basal metabolic ratio (n = 497 excluded) did not influence the results. Additional adjustment for energy density of the diet or energy intake also did not alter the associations.

DISCUSSION

The NRF index has been proposed to predict overall diet quality, but it has not yet been evaluated with respect to health outcomes. In this prospective study in elderly persons, we observed that the NRF9.3 index score—composed of nine nutrients to encourage and three nutrients to limit—was inversely associated with all-cause mortality after adjustment for potential confounders. The adjusted associations between the NRF9.3 index score and mortality were stronger in women than in men. The NRF9.3 index score tended to be inversely associated with incidence of CVD but results were not statistically significant.

In the present study, the NR9, LIM3 and NRF9.3 index scores were associated with all-cause mortality, but not with major CVD events. This could be due to the definition of the NRF9.3 index score. Food groups with a high nutrient density score on a food item level were vegetables, fruit and potatoes. However, the individual weighted NRF scores were also dependent on which food products were eaten and in which amount. Main contributors of the NRF index scores in this study were vegetables, dairy, fruit, bread and potatoes. Compared with all-cause mortality, the associations between the NRF index score and major CVD events were especially weaker for the NR9 score. Main contributors to this score were bread, fruit, vegetables, milk, fats and oils, and meat. The protective effects of fruit, vegetables and whole grains on CVD risk are well established,[29–31] but the associations of dairy with CVD are less clear.[32] Furthermore, the consumption of meat and saturated fat has been related to an increased risk of CVD and premature mortality.[33–35] Moreover, elderly persons already have more advanced atherosclerosis compared with younger persons, so that diet may not be as strongly associated with CVD at this higher age.[36] This might explain why we did not find a significant association of nutrient density and risk of CVD. Moreover, the endpoint CVD only included major CVD events. It was not possible to include minor CVD events, including angina pectoris and transient ischemic attack, and heart failure. This may have underestimated the association between the NRF index and CVD.

The inverse association between the NRF9.3 index score and mortality was stronger in women than in men. This may be due to the differences in index scores between men and women: mean NRF9.3 index score was higher and the range was wider in women and different food groups contributed to the index scores in men and women. In men, the main contributors were vegetables, potatoes and bread, whereas in women vegetables, fruit and dairy mainly contributed to the NRF9.3 index score. Moreover, men were less often never smokers and more often former smokers. Although we adjusted for smoking and smoking did not appear to be an effect modifier, we could not take into account time since quitting smoking and number of cigarettes smoked; thus, residual confounding may be present. Paradoxically, persons with prevalent hypertension and diabetes were more likely to have a higher NRF9.3 index score. It might be that these persons changed their diet due to their disease; therefore, we adjusted for doctor-prescribed diets. Although BMI is on the causal pathway of diet and disease, adjustment may also correct for misreporting by individuals with a higher BMI. Furthermore, when studying diet–disease relationships, physical activity level is also considered an important confounder. As data on physical activity were only collected in the third phase of the study, these data were available for only a subset of the population. Additional adjustment for physical activity level weakened the associations. This might be due to residual confounding. However, because the adjustment for other lifestyle factors such as smoking and alcohol strengthened the associations, it is more likely to be due to a decreased study power.

Various nutrient quality systems have been developed, but only few aimed to evaluate the nutritional quality of foods.[37] In their comparative analysis, Garsetti *et al.*[37] showed that it is difficult to find systems that are simple to use, scientifically relevant and able to cope with changes in nutrient recommendations. Azais-Bradesco *et al.*[38] compared four nutrient quality models and concluded that these models are a powerful tool to translate nutritional information related to the whole diet into the level of individual foods; however, the performance of the existing models was moderate. More recently, the Overall Nutritional Quality Index (ONQI) was developed. The ONQI aims to provide an objective and universally applicable metric to distinguish reliably among foods with low and high nutritional quality and would offer means for subjects to improve the quality of their diet and potentially their health.[39] The ONQI includes nutrients with beneficial as well as unfavorable effects on health. In contrast to the NRF index score, the ONQI also includes measures of energy density and macronutrient quality as additional adjustments. Furthermore, the ONQI score weighs the nutrients by coefficients for the prevalence of one or more conditions most strongly associated—on the basis of literature review and expert opinions—with the nutrients; the severity of those conditions; and the strength of the association between the nutrients and the conditions.[39] However, these weights were confidential and propriety information, which makes application to other countries with other food products and food choices as compared with the US difficult. Fulgoni *et al.*[13] indicated that a well-considered selection of nutrients on the basis of the best available evidence is a better alternative than *a priori* weighing of the NRF algorithms as the weighing factors are essentially arbitrary. Both the ONQI score and the NRF9.3 index score had a strong relationship with the HEI-2005.[13,40] However, the amount of explained variance of the HEI-2005 was higher for the NRF9.3 index than for the ONQI score. This suggests that the NRF9.3 index predicts overall diet quality better than the ONQI score. The ONQI score is the first system that was evaluated against health outcomes and it was shown to be inversely associated with risk of total chronic diseases, CVD, diabetes and all-cause mortality in both men and women.[41] In the present study, we found the associations with mortality to be stronger than those reported by Chiuve *et al.*[41] Because the applied weights in the ONQI score are not known, we cannot speculate on the possible causes of the observed differences for CVD.

In contrast to the HEI, the NRF index is applicable to individual foods and can at the same time provide a clear measure of the nutrient density of the overall diet.[12] Moreover, the NRF approach is not only science-based, but also consumer-driven by identifying affordable nutrient-dense foods.[11,42] By choosing nutrient-dense foods, people will be able to meet their nutrient requirements without consuming too much energy. Furthermore, the NRF index includes nutrients that have public health relevance[43] and aims to be simple and transparent.[12] However, there are several methodological issues with regard to the NRF index like the nutrients to include in the model, the choice of the reference daily values, and the choice of the reference amount.

First, we selected the NRF9.3 index score for the present study as it explained most of the variation in the HEI-2005.[13] The NRF9.3 index score is composed of a positive sub-score on the basis of protein; dietary fiber; vitamin A, C and E; calcium; iron; potassium and magnesium, and a negative sub-score on the basis of saturated fat, total or added sugar, and sodium. However, for certain specific health outcomes, other important nutrients, such as B-vitamins, long-chain polyunsaturated fatty acids or trans-fatty acids should be included in the index. When data on added sugar is not available, total sugar can be used instead. Fulgoni *et al.*[13] found lower correlations with the HEI-2005 when added sugars were replaced by total sugar. However, as the NRF9.3 index score with total sugar still explained >35% of the variation in HEI-2005, including total sugar seems a reasonable alternative. Indeed, the strength of the association between the NRF9.3 index score and all-cause mortality observed in women was not altered when total sugar was replaced with added sugar in the index score.

Second, the NRF9.3 index scores were calculated using Dutch food composition tables and European dietary reference values. As other studies may use other—country-specific—food composition tables and dietary reference values, the NRF scores for each food item and every individual will differ from country to country.

Third, we used 100 kcal as the reference amount to evaluate the nutrient density of the overall diet. The NRF index can be calculated on the basis of 100 kcal, 100 g or on serving sizes. Although each method has its advantages and disadvantages, the index on the basis of 100 kcal is preferable for the positive sub-scores.[44] Fourth, sodium intake was assessed with a food-frequency questionnaire, whereas 24-hour urine collections are considered the optimal method because added salt is not taken into account otherwise.[45]

To our knowledge, we are the first who studied the association between the NRF index, all-cause mortality and incident CVD. Future studies are needed to examine whether the observed associations also apply to other health outcomes and various population subgroups. In addition, the effect of extending the current NRF index score with other nutrients on the association with health outcomes should be examined. In conclusion, persons with a higher NRF9.3 index score, indicating more beneficial components and/or less limiting components, had a lower risk of all-cause mortality. Consuming a nutrient-dense diet may improve survival.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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DISCLAIMER

The sponsors had no input in the design, the conduct, the analysis or the interpretation of the study, and did not influence the manuscript preparation.

AUTHOR CONTRIBUTIONS

All authors had full access to all of the data (including statistical reports and tables) and take responsibility for the integrity of the data and the accuracy of the data analysis. AH and JW were responsible for study concept and design. OHF, AH and JCMW acquired the data. MTS, DS, JFvY, AG and EJMF analyzed and interpreted the data. MTS, DS and JFvY drafted the manuscript, which was critically revised for important intellectual content by all authors. MTS, DS and EJMF were responsible for the statistical analysis. EJMF supervised the study and is guarantor.

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