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Metabolic syndrome-related dietary pattern and risk of mortality in kidney transplant recipients

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Abstract *Background and aims:* Presence of the metabolic syndrome (MetS) importantly contributes to excess mortality in kidney transplant recipients (KTRs). However, it is unclear which dietary factors drive the adverse role of MetS in KTRs. We aimed to define a dietary pattern that maximally explained the variation in MetS components, and to investigate the association between this MetS-related dietary pattern (MetS-DP) and all-cause mortality in KTRs.
Methods and results: We included 429 adult KTRs who had a functioning graft ≥1 year. A MetS-DP was constructed using habitual dietary intake derived from a 177-item food frequency questionnaire. We used reduced rank regression (RRR), and defined the six components of MetS (waist circumference, systolic blood pressure, diastolic blood pressure, serum triglycerides, HbA1c, and HDL cholesterol) as response variables and 48 food groups as predictor variables. We evaluated the association between the MetS-DP and all-cause mortality using multivariable Cox regression analysis. The MetS-DP was characterized by high intakes of processed meat and desserts, and low intakes of vegetables, tea, rice, fruits, milk, and meat substitutes. During a mean follow-up of 5.3 ± 1.2 years, 63 KTRs (14.7%) died. Compared to the lowest tertile of the Mets-DP score, those with the greatest adherence had a more than 3-fold higher risk of all-cause mortality (hazard ratio [HR] = 3.63; 95% confidence interval [CI], 1.70–7.74, $P < 0.001$), independent of potential confounders.
Conclusions: We identified a MetS-related dietary pattern which was independently associated with all-cause mortality in KTRs. The association between this dietary pattern and all-cause mortality was mediated by MetS.
Clinical trial reg. no. NCT02811835

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Introduction

The metabolic syndrome (MetS) is defined as a combination of abdominal obesity, hypertension, dyslipidemia, and abnormal fasting glucose level or impaired glucose tolerance [1]. Evidence shows that MetS and its components are associated with mortality, cardiovascular disease, diabetes and kidney disease in the general population [2–4]. In the setting of kidney transplant recipients (KTRs), more than half of the KTRs may suffer from MetS in the long term [5], which increases the risk for posttransplantation diabetes, graft failure and poor survival after kidney transplantation [6].

MetS entails a cluster of modifiable factors that may be targeted by dietary interventions [7]. Several approaches may be used to identify dietary patterns, including hypothesis-oriented approaches, e.g., Mediterranean diet score, exploratory approaches e.g., principal component analysis (PCA), or a mix of both e.g., reduced rank regression (RRR) [8–10]. A dietary pattern obtained by RRR was proven to be strongly associated with the prevalence of MetS in the general population [10]. In KTRs, the Mediterranean diet was found to be associated with a lower incidence of MetS one year after kidney transplantation [11]. Moreover, both the Mediterranean diet [12,13] and Dietary Approach to Stop Hypertension (DASH) diet [14] were found to be associated with kidney function decline and all-cause mortality after kidney transplantation. However, the role of MetS as a mediator in the association of diet with the prognosis of KTRs is still unknown.

The RRR method to generate dietary patterns was proposed by Hoffmann et al. [15]. In contrast with PCA analysis, RRR produces a linear combination of food groups that maximally explain variations in disease-related intermediate response variables. Thus, RRR can be used to test specific hypotheses regarding the potential pathways (intermediate risk factors) by which diet may influence disease outcomes [16]. In the present study, we aimed to apply RRR to derive a dietary pattern that maximized the explained variation in the components of MetS. Subsequently, we investigated whether this MetS-related dietary pattern (MetS-DP) was associated with all-cause mortality prospectively in KTRs.

Methods

Study design and population

All KTRs (≧18 years old) with a functioning graft for at least 1 year who visited the outpatient clinic of University Medical Center Groningen (UMCG, Groningen, the Netherlands) between November 2008 and May 2010 were invited to participate in this prospective cohort study. The detailed information on this cohort was described previously [17]. Baseline data was obtained at least one year after transplantation. Among 817 invited KTRs, 707 (86.5%) signed written informed consent to participate in this cohort study. Those with diabetes mellitus at baseline or before transplant (n = 180) were excluded in this study. The reason for this was to eliminate the influence of reverse causality between diet and diabetes mellitus. Participants with missing dietary data (n = 55) and missing values of MetS parameters (waist circumference, systolic blood pressure, diastolic blood pressure, serum triglycerides, HbA1c, and HDL cholesterol, n = 40) at baseline were excluded. Three patients with implausible energy intake were excluded, resulting in 429 participants eligible for analysis. This study was conducted according to the guidelines settled in the Declaration of Helsinki and the Declaration of Istanbul on Organ Trafficking and Transplant Tourism. This research project was approved by the institutional review board of the UMCG (METc 2008/186).

Assessment of dietary intake

Dietary intake was evaluated at baseline by a validated self-administered food frequency questionnaire (FFQ) developed by Wageningen University [18]. The FFQ contains questions on frequency and number of servings of 177 food items consumed during the last four weeks. A trained researcher checked the FFQ for the completeness and verified inconsistencies with the patients on the day of the visit to the outpatients clinic. The implementation and detailed information of FFQ was described previously [19]. Total energy intake and nutrient intake per day were determined using the Dutch Food Composition Table of 2006 (NEVO 2006) [20]. To evaluate for implausible energy intake, the ratio between energy intake (EI) and basal metabolic rate (BMR, calculated by the Schofield equation [21]) was used to evaluate the reliability of dietary intake. EI/BMR $<0.5->2.75$ were considered unreliable; EI/BMR between 0.5 and 2.75 were considered reliable [22,23]. Food items were classified into 48 food groups based on similarities in food and nutrient composition (Table S1). For each of the 48 food groups, intakes were presented as the gram per day.

Assessment of clinical variables

Baseline data were collected during the visit to the outpatient clinic after 8–12 h of the fasting period. Blood pressure was measured using a semiautomatic device (Dinamap1846; Critikon, Tampa, FL, USA). Waist circumference was measured on bare skin at the midpoint between the 10th rib and the iliac crest. Participants were informed to provide fasting blood samples and were instructed to collect a 24-hour urine sample at baseline. Blood and urine laboratory assessments were performed according to routine laboratory methods. eGFR was calculated using the creatinine-based Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI) [24]. Self-administered questionnaires were used to assess health-related behaviors such as smoking status and physical activity. Smoking was categorized as current smokers and non-current smokers. Daily physical activity was derived using the Short Questionnaire to Assess Health enhancing physical activity (SQUASH) score (time × intensity) [25]. Information on transplantation

characteristics, medical history, and medication use were obtained from patient records. The MetS was defined, according to the National Cholesterol Education Program Expert Panel [26], as the presence of at least three of the following components: (1) central obesity (waist circumference >102 cm in men, >88 cm in women); (2) elevated blood pressure systolic blood pressure (SBP) ≧ 130 or diastolic blood pressure (DBP) ≧85 mmHg or use antihypertensive medications; (3) elevated serum triglycerides level (≧1.70 mmol/L) or use lipid-lowering medications; (4) elevated fasting glucose level (fasting plasma glucose≧6.1 mmol/L) or use anti-diabetic medications; (5) reduced HDL cholesterol level (<1.03 mmol/L in men, <1.29 mmol/L in women).

Outcomes

The primary outcome of this study was all-cause mortality. The secondary outcome of this study was kidney function decline, defined as doubling of serum creatinine and/or death-censored graft failure. Doubling of serum creatinine was defined as the first serum creatinine value that was twice the baseline value. Graft failure was defined as return to hemodialysis or retransplantation. Endpoints were recorded from baseline measurement until September 30, 2015.

Statistical analysis

To derive a dietary pattern, RRR was performed by using PLS procedure in SAS (version 9.4; SAS Institute, Cary, NC). Hoffmann et al. described the RRR method in detail previously, including SAS code and its application in nutritional epidemiology [15]. Briefly, RRR determines linear functions of predictor variables (food groups) by maximizing the explained variation in the response variables (intermediate risk factors for disease). In the RRR model, two types of observed variables were distinguished in this study: the predictor variables (48 food groups) and the response variables (6 components of MetS: waist circumference, systolic blood pressure, diastolic blood pressure, serum triglycerides, HbA1c, and HDL cholesterol). Due to the non-normal distribution of serum triglycerides, HbA1c, and HDL cholesterol, Ln-transformation were applied before performing the RRR. Within the RRR procedure, factor loadings are estimated to describe the contribution of the particular food groups to the dietary pattern score. Factor loading can range from −1 to 1, with |1| implicating that the full dietary pattern is explained by the food group. Hence, an absolute higher factor loading value indicates that the food group contributes more to the dietary pattern. We considered food groups with absolute factor loading ≧0.2 to be relevant contributors to the dietary pattern [27−30]. The dietary pattern score is calculated as the sum of z-standardized consumptions (mean = 0, standard deviation = 1) of 48 food groups multiplied by an individual weight (factor loading). Food groups that are not consumed are not included in the dietary pattern score for that individual. Six dietary patterns were identified by RRR analysis in this study because the number of extracted dietary patterns is in accordance with the number of response variables. We considered the first dietary pattern because it explained most variation in response variables. Given that dietary patterns vary between populations, a simplified dietary pattern score was constructed in order to improve comparability and interpretability. The simplified MetS-DP score, which is reported throughout the current paper, was calculated by summing up the weighted standardized food intakes (g/day) with absolute factor loadings ≧0.2 [27]. The simplified MetS-DP score was then categorized into tertiles, whereby the highest tertile was composed of KTRs whose diets conformed most closely to this dietary pattern.

We examined baseline characteristics of the KTRs across tertiles of the simplified MetS-DP score. P for trend over the tertiles of the simplified MetS-DP score was calculated by linear regression analysis for continuous variables or Cochran-Armitage Trend Test for categorical variables. Post-hoc pairwise comparison with Holm−Bonferroni adjustment to the p-value was performed (T2 vs. T1 and T3 vs. T1). In the prospective analysis, Cox regression was used to evaluate the association between the simplified MetS-DP score and all-cause mortality and kidney function decline adjusted for potential confounders. Hazard ratios (HR) and 95% confidence intervals (CI) were calculated across tertiles of the simplified MetS-DP score. We selected the confounders based on the clinical relevance and literature [14,31]. In the models, initially, we adjusted for age and sex (Model 1). Then, kidney parameters, i.e, eGFR, proteinuria (≧0.5 g/day), and time between transplantation and baseline measurement were added (Model 2). In Model 3, we additionally adjusted for the presence of MetS and prednisolone dose. In Model 4, health-related behavior variables including physical activity, smoking, and total energy intake were additionally included. Finally, BMI, cardiovascular disease history, and systolic blood pressure were further added as model 5. The association of the continuous simplified MetS-DP score with mortality in KTRs is visualized by fitting multivariable Cox regression analyses according to model 5 using the median value of the simplified MetS-DP score as the reference value. The statistical analyses were conducted using R version 3.4.2 (Vienna, Austria). A two-tailed P value < 0.05 was considered statistically significant.

Results

Of the 429 KTRs included in this study, 56.5% were men. The presence of the MetS at baseline was 54.1%. The mean values (±SD) of waist circumference, SBP, DBP, HbA1c, serum triglycerides, and HDL cholesterol were 99.1 ± 12.0 cm in men and 92.2 ± 14.6 cm in women, 135 ± 17 mmHg, 83 ± 11 mmHg, 5.7 ± 0.4%, 1.8 ± 0.9 mmol/L, 1.4 ± 0.5 mmol/L, respectively.

MetS-related dietary pattern (MetS-DP)

The MetS-DP explained 5.7% of the joint variation in the combination of 6 components of MetS. For the MetS

components individually, the MetS-DP explained 9.5% of the variation in waist circumference, 8.7% in DBP, 6.1% in SBP, 5.1% in HDL cholesterol, 4.1% in HbA1c, and 0.8% in triglycerides. All 48 food groups were ranked by decreasing factor loadings (Table S2).

Eight food groups with an absolute factor loading ≱0.2 were considered to be the main contributors to the MetS-DP (Table 1). The MetS-DP was characterized by high intakes of processed meat and desserts, and low intakes of vegetables, tea, rice, fruits, whole milk, and meat substitutes. Table 1 shows the factor loadings and the median intakes of the eight most important food groups across tertiles of the simplified MetS-DP score.

Baseline characteristics across tertiles of the simplified MetS-DP score

Baseline characteristics across tertiles of the simplified MetS-DP score are shown in Table 2. At baseline, KTRs in the highest tertile were younger, predominantly men, with higher waist circumference, higher BMI, higher blood pressure, higher HbA1c, higher triglyceride, and lower HDL cholesterol compared to the lower tertiles. No differences in kidney function were found among the tertiles, nor did we find differences in the use of antihypertensives, statin, and immunosuppressive uses across the tertiles. The proportion of current smokers was higher in the highest tertile compared to lower tertiles.

The simplified MetS-DP score and outcomes

The mean follow-up time was 5.3 ± 1.2 years, and 63 (14.7%) participants died during follow up. Cardiovascular disease (33.3%) and infections (28.5%) were the most common causes of mortality in this study. Results of the prospective association between the simplified MetS-DP score and all-cause mortality are shown in Table 3. After adjustment for all relevant confounders, patients in the highest tertile of simplified MetS-DP score had a higher risk of all-cause mortality compared with the lowest tertile (HR 3.63 [95% CI 1.70−7.74], $p < 0.001$). The same association were seen between an increase of the continuous simplified MetS-DP score and all-cause mortality (HR 1.81 [95%CI 1.31−2.50], $p < 0.001$). The correlation of the continuous simplified MetS-DP score with all-cause mortality by using multivariable Cox regression analyses is illustrated in Fig. 1. However, no significant associations were found between simplified MetS-DP and the outcome of graft failure or the composite outcome of graft failure or doubling of serum creatinine (Table S3).

Discussion

In the present study, we defined a MetS-DP that maximally explained the variation in MetS components and was characterized by high intakes of processed meat and desserts, and low intakes of vegetables, tea, rice, fruits, whole milk, and meat substitutes. This dietary pattern was significantly and unfavorably associated with all-cause mortality, independent of other potential risk factors in KTRs. To our knowledge, this is the first study applying RRR to identify a MetS-DP in KTRs. This finding suggests that the association between this dietary pattern and all-cause mortality was mediated by MetS.

After transplantation, more than half of KTRs developed MetS and it is one of the major risks for the mortality and graft failure of KTRs [5]. MetS contains a cluster of modifiable factors that may be influenced by several different factors, such as the time after transplantation, kidney function, side effects of immunosuppressive medications, and lifestyle modification [32−34]. Diet plays an important role in the development of MetS in KTRs. Nafar et al. [11] found that the Mediterranean dietary pattern was associated with lower risks of MetS, whereas fat and sugar dietary pattern derived by factor analysis was associated with higher risks of MetS in KTRs. In addition, vegetable intake was found to be associated with lower risk of posttransplantation diabetes, which was mediated by the components of the metabolic syndrome [35]. In our MetS-DP generated by RRR, higher intakes of processed meat

Table 1 The factor loadings and the median intakes of the eight most important food groups across tertiles of the simplified MetS-DP score.

Food groups [a]	Factor loading[b]	Tertiles of simplified MetS-DP score[c]				
		total	T1	T2	T3	P-value for trend
High intake (g/day)						
Processed meat	0.26	12.9 (5.1−22.6)	6.6 (0.2−14.4)	11.7 (5.7−21.0)	21.9 (13.2−34.4)	<0.001
Desserts	0.25	10.2 (0−51.8)	0 (0−20.7)	0 (0−45.0)	46.0 (0−91.3)	<0.001
Low intake (g/day)						
Vegetables	−0.33	83.2 (54.4−122.3)	124.5 (85.0−161.9)	86.3 (56.0−110.0)	59.5 (36.2−78.1)	<0.001
Tea	−0.33	250.0 (53.6−500.0)	375.0 (223.1−687.5)	250.0 (89.3−375.0)	71.4 (0−250.0)	<0.001
Rice	−0.28	16.0 (4.0−32.0)	24.0 (10.0−48.0)	15.0 (5.0−24.0)	8.0 (0−20.0)	<0.001
Fruits	−0.25	123.0 (59.9−232.0)	220.5 (107.5−262.5)	135.3 (82.9−232.0)	58.1 (19.4−123.0)	<0.001
Whole milk	−0.23	16.0 (0.4−40.0)	20.0 (0.4−60.3)	16.0 (0.4−32.0)	16.0 (0.4−40.0)	<0.001
Meat substitutes	−0.22	0 (0−0)	0 (0−10.6)	0 (0−0)	0 (0−0)	<0.001

Data are shown with median and interquartile range (25%−75%).
[a] Data restricted to food groups with absolute factor loading ≱0.2.
[b] Factor loading was obtained directly by reduced rank regression.
[c] Simplified dietary pattern score was the sum of the weighted standardized food variables with high factor loadings (≱0.2).

Table 2 Baseline characteristics based on tertiles of the simplified MetS-DP score.

	Tertiles of simplified MetS-DP score				
	total	T1	T2	T3	P-value for trend
Demographics					
Age, years	51.2 ± 13.3	52.7 ± 12.1	52.6 ± 14.2	48.2 ± 13.2*	0.005
Sex, male (%)	56.5	39.9	55.9*	73.4*	<0.001
Metabolic parameters					
MetS (%)	54.1	48.3	56.6	57.3	0.123
Cardiovascular disease history (%)	8.2	8.4	5.6	10.5	0.517
Waist circumference, cm					
Men	99.1 ± 12.0	96.2 ± 10.6	98.5 ± 13.7	101.2 ± 11.0*	0.033
Women	92.2 ± 14.6	89.8 ± 13.3	94.1 ± 15.2	94.5 ± 15.8	0.113
BMI	25.9 ± 4.4	25.1 ± 3.8	26.0 ± 5.0	26.5 ± 4.2*	0.017
SBP, mmHg	135 ± 17	131 ± 16	137 ± 17*	137 ± 17*	0.004
DBP, mmHg	83 ± 11	80 ± 11	84 ± 10*	85 ± 11*	<0.001
HbA1c (%)	5.7 ± 0.4	5.6 ± 0.4	5.7 ± 0.4	5.7 ± 0.4*	0.038
Fast plasma glucose, mmol/L	5.2 ± 0.6	5.1 ± 0.7	5.2 ± 0.6	5.2 ± 0.7	0.319
HDL cholesterol, mmol/L	1.4 ± 0.5	1.6 ± 0.7	1.4 ± 0.4*	1.3 ± 0.4*	<0.001
LDL cholesterol, mmol/L	3.0 ± 0.9	2.9 ± 0.9	3.0 ± 0.9	3.1 ± 1.0	0.463
Total cholesterol, mmol/L	5.1 ± 1.1	5.1 ± 1.1	5.1 ± 1.0	5.1 ± 1.2	0.889
Triglycerides, mmol/L	1.8 ± 0.9	1.7 ± 0.7	1.8 ± 0.9	1.9 ± 1.0*	0.017
hs-CRP, mg/L	1.4 (0.6–3.8)	1.2 (0.6–3.5)	1.4 (0.5–4.3)	1.6 (0.6–3.9)	0.567
Urinary creatinine excretion, mmol/24 h	11.8 ± 3.3	10.7 ± 2.8	11.6 ± 3.1*	13.2 ± 3.6*	<0.001
Kidney function					
Serum creatinine, umol/L	137.2 ± 60.7	131.3 ± 54.2	137.9 ± 58.8	142.2 ± 68.1	0.310
eGFR, mL/min/1.73 m^2	53.4 ± 20.2	52.7 ± 19.0	52.5 ± 21.2	54.8 ± 20.3	0.566
Proteinuria, g/24 h	0.18 (0.02–0.31)	0.16 (0.02–0.28)	0.18 (0.02–0.34)	0.20 (0.02–0.42)	0.078
Proteinuria ≱0.5 g/day, (%)	20.3	14.7	23.1	23.1	0.106
Kidney transplantation characteristics					
Time between transplantation and baseline measurement, year	5.2 (2.2–12.2)	6.1 (3.1–14.0)	6.2 (2.0–12.7)	4.6 (1.4–10.3)	0.071
Pre-emptive transplant, (%)	19.1	18.9	21.0	17.5	0.764
Living donor (%)	37.1	37.1	35.7	38.5	0.807
Acute rejection (%)	23.5	28.0	21.7	21.0	0.163
Medication (%)					
Statin	48.3	51.0	46.9	46.9	0.478
Antihypertensives	85.5	83.9	85.3	87.4	0.400
Tacrolimus	15.2	15.4	12.6	17.5	0.621
Cyclosporine	36.4	32.2	37.8	39.2	0.219
Mycophenolate mofetil	67.8	65.7	67.1	70.6	0.376
Prednisolone	99.3	98.6	100	99.3	0.478
Prednisolone dose, mg/day	5.7 ± 3.3	6.1 ± 3.4	5.9 ± 3.3	5.2 ± 3.2	0.085
Lifestyle behaviors					
Total energy intake, kcal/day	2195 ± 606	2240 ± 609	2083 ± 552	2261 ± 642	0.024
Total protein intake	81.6 ± 19.4	84.8 ± 19.9	79.5 ± 16.8	80.5 ± 21.0	0.048
Total fat intake	88.3 ± 31.4	89.1 ± 33.7	82.0 ± 27.8	93.8 ± 32.5	0.006
Total carbohydrate intake	254.1 ± 77.5	262.3 ± 77.1	243.4 ± 71.5	256.6 ± 82.8	0.107
Physical activity, hours × intensity	6158 ± 4394	6143 ± 3944	6082 ± 4337	6249 ± 4878	0.949
Current smoker (%)	13.5	7.1	10.1	23.4*	<0.001

Data are represented as mean ± SD, median (interquartile range), or percentage.
"*" represents $p < 0.05$ (post-hoc pairwise comparison with Holm–Bonferroni adjustment to the p-value, T2 vs. T1 and T3 vs. T1).
Abbreviation: MetS, metabolic syndrome; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein.

and desserts and lower intakes of fruits and vegetables were found to be associated with higher blood pressure, higher waist circumference, higher triglyceride, and lower HDL cholesterol, which are the components of MetS, suggesting that the MetS-DP derived by RRR was consistent with the previous evidence. The presence of MetS at baseline was not significantly different across the tertiles of MetS-DP score, which is probably explained by the fact that the MetS-DP was based on the different components of MetS rather than the presence of MetS. Since the components of MetS may be affected by age, sex, and medication, we additionally identified a dietary pattern using age-, sex- and medication-adjusted components of MetS as response variables. The dietary pattern was similar (data not shown) to the unadjusted pattern, suggesting the stability of this dietary pattern. The derived dietary pattern in our study seems logically intuitive, considering the dietary guidelines for the general population. However, data on dietary behavior and diet-disease relationship in KTRs are still scarce, and straightforward

Table 3 Risk of all-cause mortality according to the simplified MetS-DP score by Cox regression.

	Tertiles of simplified MetS-DP score HR (95% CI)				Continuous simplified MetS-DP score	
	T1	T2	T3	P for trend	HR (95% CI)	P-value
Mortality, n (%)	11/143 (7.7)	26/143 (18.2)	26/143 (18.2)	0.012	63/429 (14.7)	-
Crude	1.00	2.57 (1.27−5.20)	2.63 (1.30−5.33)	0.009	1.45 (1.11−1.90)	0.007
Model 1	1.00	2.62 (1.29−5.32)	3.56 (1.74−7.27)	<0.001	1.72 (1.29−2.30)	<0.001
Model 2	1.00	2.40 (1.17−4.92)	3.41 (1.66−7.00)	<0.001	1.67 (1.24−2.24)	<0.001
Model 3	1.00	2.41 (1.17−4.96)	3.35 (1.62−6.91)	<0.001	1.64 (1.22−2.20)	<0.001
Model 4	1.00	2.17 (1.05−4.50)	3.18 (1.53−6.63)	0.002	1.68 (1.23−2.30)	0.001
Model 5	1.00	2.36 (1.13−4.90)	3.63 (1.70−7.74)	<0.001	1.81 (1.31−2.50)	<0.001

Model 1: adjusted for age and sex.
Model 2: Model 1 + eGFR, proteinuria (≧0.5 g/day), and time between transplantation and baseline measurement.
Model 3: Model 2 + presence of MetS at baseline and prednisolone dose.
Model 4: Model 3 + total energy intake, smoking and physical activity.
Model 5: Model 4 + BMI, cardiovascular disease history, and systolic blood pressure.

extrapolation of findings in the general population to KTRs is not warranted, considering the differences in disease load and the possible metabolic adverse effects of steroids and tacrolimus [36,37]. Therefore, our findings support the importance of dietary factors in MetS in KTRs, notwithstanding the concomitant presence of other metabolic risk factors. Moreover, this pattern characterized by high intakes of sweet and fat products and low intakes of fruits and vegetables is associated with the risk of all-cause mortality after kidney transplantation.

Dietary predictors for the prognosis of KTRs have been studied at many levels, including nutrients, foods, and dietary patterns. As people do not consume isolated nutrients, dietary patterns may be more informative because they address the effect of the diet as a whole, providing a broader picture of habitual dietary behavior [38]. Previously, Mediterranean style diet (rich in fruit, vegetables, legumes, cereals, nuts, and fish, and poor in meat, poultry, and dairy products) was found to be associated with lower risks of new-onset diabetes, kidney function loss and all-cause mortality in KTRs in the same cohort [12,13]. Furthermore, we found that DASH diet (high intakes of fruits, vegetables, and whole-grain, low-fat dairy products, legumes and nuts, and low intakes of sodium, sweetened beverages, and red processed meat) is also associated with lower risks of both kidney function decline and all-cause mortality in KTRs [14]. However, these dietary patterns are pre-defined based on dietary recommendations and are most often not disease-specific. Thus, they may not reflect how people really eat and how those patterns are associated with disease outcomes. The dietary pattern derived by RRR shows the combinations of foods that are most relevant for the intermediate risk factors (in this case MetS). Accordingly, the RRR method is useful to test hypotheses regarding the potential pathways through which diet may influence disease outcomes [15,16]. As such, RRR could be considered more suitable than classic data-driven methods, for example, PCA which does not take intermediate disease-related risk factors into account. Accordingly, RRR is better suited to identify dietary patterns that are related to disease-specific risk factors. This assumption is supported by several head-to-head comparisons of RRR versus PCA [39,40]. By RRR, we found that MetS-DP explained 5.7% of the joint variation in the combination of 6 components of MetS, and for the separate components of MetS, the explained variance ranged between 0.8 and 9.5%. Whereas the explained variance may seem modest or even low. We want to point out that MetS components, which were considered as intermediate risk factors, were used to identify MetS-DP. The association of MetS-DP with mortality, rather than the nominal magnitude of variation of MetS explained, determines the clinical significance of our findings. Nevertheless, the simplified MetS-DP was associated with a more than 3-fold higher all-cause mortality risk. Our results suggest that the association between the dietary pattern and mortality was mediated by MetS.

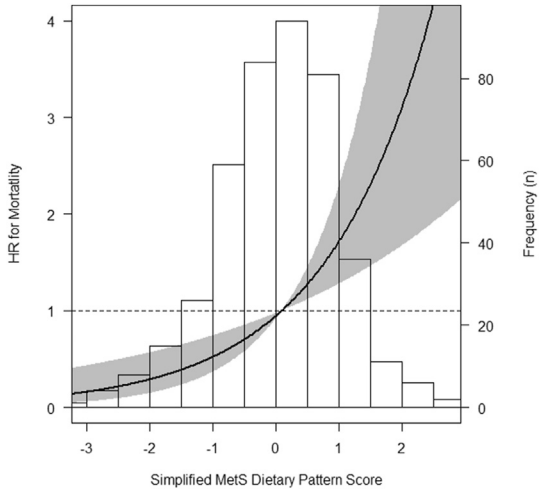

Figure 1 The association of simplified MetS-DP score with mortality in KTRs. Data were fit by a Cox proportional hazards regression using the median value of simplified MetS dietary pattern score as the reference value (hazard ratio = 1). The hazard ratio was adjusted for age, sex, eGFR, and proteinuria (≧0.5 g/day), time between transplantation and baseline measurement, presence of MetS at baseline, prednisolone dose, total energy intake, smoking, physical activity, BMI, cardiovascular disease history, and systolic blood pressure. The black line represents the adjusted hazard ratio and the grey area represents the 95% confidence interval.

The potential mechanism underlying the deleterious effect of the MetS-DP on the prognosis of the KTRs may be associated with the cardiovascular event after transplantation. The MetS-DP was derived based on the six components of MetS that are also risk factors for cardiovascular disease. Cardiovascular disease and infections/sepsis were found to be the most common causes of mortality in KTRs [41]. The cardiovascular events causing mortality in our study was accounting for 33.3%. Beyond this, the Mediterranean style diet (rich in fruits and vegetables and poor in meat and dairy products) was proven to attenuate the cardiovascular risks [42]. The MetS-DP (low in fruits and vegetables) which is somewhat opposite of the Mediterranean diet may thus have an adverse effect on cardiovascular disease. Moreover, there is evidence of increased oxidative stress and inflammation in patients with cardiovascular disease, metabolic syndrome and kidney transplantation [42–44]. Dietary patterns poor in natural antioxidants and fiber from fruits, vegetables may activate the innate immune system [45].

The main strength of this study is that we constructed a dietary pattern that explained the maximum variations of six components of MetS, in a well-documented population without loss to follow-up. We clearly showed a deleterious role for MetS-DP in the all-cause mortality, which suggested a potential intermediate pathway between diet and disease outcome. However, several limitations should be also noted when interpreting the results in the present study. First, the MetS-DP explained only a small percentage (5.7%) of the variation in components of MetS. This may partly be inherent to this type of analysis. Whereas studies with nutrients as response variables tended to have a higher explained variation compared to those with biomedical risk factors as response variables [15,46], our results are comparable with or better than other studies using components of MetS as the response variables [40,47]. Second, a substantial number of patients were excluded in this study because they had diabetes mellitus at baseline or before transplantation. Whereas this is useful to reduce the risk of reverse causality, it limits the generalizability of our data. Third, this is a single-center and observational study, and the results need to be validated by other studies. As the nutritional guidelines for KTRs are limited, higher quality studies like randomized controlled trials focused on the dietary patterns are needed to substantiate new evidence based guidelines.

In conclusion, a MetS-DP characterized by high intakes of processed meat and desserts, and low intakes of vegetables, tea, rice, fruits, whole milk, and meat substitutes was independently associated with a higher risk of all-cause mortality in KTRs. Our study paves the way for prospective studies addressing whether a dietary pattern that is linked to metabolic syndrome might influence mortality after kidney transplantation.

Clinical trial registration number

Jun 23, 2016, Clinical trial reg. no. NCT02811835, ClinicalTrials.gov.

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Conflicts of interest

The authors declare no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.numecd.2021.01.005.

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