

# The Association between a Mediterranean-Style Diet and Kidney Function in the Northern Manhattan Study Cohort

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## Abstract

**Background and objectives** Various dietary strategies have been investigated to slow kidney function decline. However, it is unknown whether a Mediterranean diet, which has been associated with improved cardiovascular risk, is associated with change in kidney function.

**Design, setting, participants, & measurements** This study used the Northern Manhattan Study, a prospective, multiethnic, observational cohort of participants who were stroke free at baseline. Data were collected between 1993 and 2008. Serum creatinine measurements were taken a mean 6.9 years apart. A baseline dietary questionnaire was extrapolated into a previously used 9-point scoring system (MeDi). The primary outcome was incident eGFR < 60 ml/min per 1.73 m<sup>2</sup> using the Modification of Diet in Renal Disease formula. A secondary outcome was the upper quartile of annualized eGFR decline ( $\geq 2.5$  ml/min per 1.73 m<sup>2</sup> per year). Conditional logistic regression models adjusted for demographics and baseline vascular risk factors.

**Results** Mean baseline age was 64 years, with 59% women and 65% Hispanics (N=900); mean baseline eGFR was 83.1 ml/min per 1.73 m<sup>2</sup>. Incident eGFR < 60 ml/min per 1.73 m<sup>2</sup> developed in 14%. In adjusted models, every 1-point increase in the MeDi score, indicating increasing adherence to a Mediterranean diet, was associated with decreased odds of incident eGFR < 60 ml/min per 1.73 m<sup>2</sup> (odds ratio, 0.83; 95% confidence interval, 0.71 to 0.96) and decreased odds of being in the upper quartile of eGFR decline (odds ratio, 0.88; 95% confidence interval, 0.79 to 0.98).

**Conclusions** A Mediterranean diet was associated with a reduced incidence of eGFR < 60 ml/min per 1.73 m<sup>2</sup> and upper quartile of eGFR decline in a multiethnic cohort.

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## Introduction

CKD is a growing epidemic resulting in substantial morbidity, mortality, and economic costs (1,2). Although there has been significant progress in protecting against kidney disease and its progression through aggressive treatment of established traditional risk factors such as hypertension (3), diabetes (4), and proteinuria (5), kidney function still declines over time. Ascertaining other modifiable risk factors that may modulate CKD incidence or progression could assist prevention and treatment strategies.

One such risk factor is diet. There is mounting evidence that poor dietary patterns may lead to kidney disease (6,7). Until recently, dietary studies in CKD have focused mainly on protein intake, which have suggested a modest benefit with protein restriction (8,9). The effect of other dietary patterns on kidney function is unclear. The Mediterranean diet has received attention for ameliorating cardiovascular risk in observational studies (10,11) and randomized trials (12,13). Purported mechanisms of action, including

improvements in BP (14,15), lipid profile (15), endothelial function (16), and inflammation (17), may benefit the kidney as well. Few studies have examined relationships between a Mediterranean-style diet and kidney function, but their results are inconclusive due to cross-sectional study design (18–21), limited demographics (6,18), or short duration (22). The purpose of this observational analysis was to characterize the effect of varying degrees of a Mediterranean-style diet on long-term kidney function in a community-based, prospective cohort. We hypothesized that increased adherence to a Mediterranean diet would be associated with a decreased loss of kidney function.

## Materials and Methods

### Selection of Prospective Cohort

The Northern Manhattan Study (NOMAS) is a prospective, multiethnic, community-based cohort of 3298 participants recruited from a geographic area of northern Manhattan, New York. The details of recruitment

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and assessment were previously described (23). Briefly, participants were enrolled between 1993 and 2001, and were eligible if they met the following criteria: no prior history of stroke, age >40 years, and residence in a household with a telephone in northern Manhattan. The institutional review boards of Columbia University and University of Miami approved the study.

### Baseline Evaluation and Follow-Up

Demographic, laboratory, and medical history data were collected at baseline enrollment. Participants were followed annually starting in 1998. From 2003 to 2008, a subgroup of 1091 participants from the original cohort was recruited into a brain magnetic resonance imaging (MRI) substudy. In order to be eligible for this substudy, participants had to be clinically free of stroke, free of contraindications to MRI, aged at least 55 years, and able to sign informed consent. A new set of laboratory data, including serum creatinine, were collected upon enrollment.

Inclusion criteria for this analysis included all participants enrolled in the MRI substudy. The final sample size was 900, because participants were excluded if they did not have two serum creatinine measurements ( $n=81$ ) or were lacking baseline dietary assessment ( $n=110$ ).

### Assessment of Kidney Function and Outcomes

Serum creatinine was measured using the Jaffé reaction. Kidney function was estimated using the Modification of Diet in Renal Disease (MDRD) formula for eGFR as follows:

$$\text{eGFR} = 186.3 \times (\text{serum creatinine}^{-1.154}) \times (\text{age}^{-0.203}) \\ \times (0.742 \text{ for women}) \times (1.21 \text{ for blacks})$$

Few participants ( $n=41$ ) had serum creatinine measurements that were standardized to the isotope dilution mass spectrometry reference and the eGFR was calculated by the following formula (24):

$$\text{eGFR} = 175 \times (\text{serum creatinine}^{-1.154}) \times (\text{age}^{-0.203}) \\ \times (0.742 \text{ for women}) \times (1.21 \text{ for blacks})$$

Participants had their eGFR assessed at the time of original enrollment, as well as at the time of enrollment into the MRI substudy. The MDRD formula was used instead of the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) (25) because of a lack of standardized creatinine values in all participants.

The primary outcome of incident eGFR <60 ml/min per 1.73 m<sup>2</sup> was defined as participants who started with an eGFR ≥60 ml/min per 1.73 m<sup>2</sup> at baseline, and had an eGFR <60 ml/min per 1.73 m<sup>2</sup> on follow-up. Absolute change in kidney function was evaluated as an annualized rate of change in the eGFR. We also created a dichotomized variable using a cutoff of the upper quartile of annualized eGFR decliners within this cohort, a threshold used previously that portends a higher risk of cardiovascular disease (26). For the primary outcome of incident eGFR <60 ml/min per 1.73 m<sup>2</sup>, 97 participants had an eGFR <60 ml/min per 1.73 m<sup>2</sup> at baseline and were excluded ( $n=803$  for this analysis). These participants, however, were included in the outcomes involving continuous

annualized eGFR decline and upper quartile of annualized eGFR decline.

### Measurement of Other Covariates

Demographic variables and well established baseline risk factors for CKD progression were assessed as previously described and included in multivariable regression models (23). Race/ethnicity was based on self-identification. Educational status was dichotomized based on completion of high school. Insurance status was classified as having Medicaid/no insurance versus other (Medicare or private insurance). Hypertension was considered present if BP exceeded 140/90 based on an average of two measurements during initial evaluation, self-reported history of hypertension, or baseline antihypertensive medication use. Cigarette smoking status was categorized as never smoked, prior smoking, or current smoking within the last year. Fasting HDL cholesterol and calculated LDL cholesterol were included. Diabetes mellitus was present if participants had a self-reported history, used oral hypoglycemic agents or insulin, or fasting blood sugar was measured to be at least 126 mg/dl. Physical activity was based on exercise questionnaires. Body mass index was calculated as follows: (weight in kilograms/ [height in meters×height in meters]). Analyses were also adjusted for baseline use of either angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs).

### Diet

At baseline, participants were administered a modified Block National Cancer Institute food frequency questionnaire (27) to assess dietary patterns over the preceding year. Responses were converted to a Mediterranean Diet (MeDi) score as previously described (11,28,29). Kilocalorie intake was regressed and residuals of daily gram intake were calculated for the following components: dairy, meat, fruit, vegetables (excluding potatoes), legumes, cereals, and fish (28). Participants were assigned a value of 1 for each beneficial category (fruit, vegetables, legumes, cereals, and fish) in which consumption was at least as high as the sex-specific median. A value of 1 was assigned if daily intake was below the sex-specific median for the detrimental food groups (dairy and meat). In addition, 1 point each was added for moderate alcohol consumption and a dietary ratio of monounsaturated fats to saturated fats that was at or above the median. Moderate alcohol consumption was defined as drinking two or fewer drinks per day (30). In total, there were nine components of the MeDi score, which ranged from 0–9, with higher scores representing greater similarity to a Mediterranean diet. Approximately 84% of the entire NOMAS cohort had sufficient data to calculate a MeDi score.

### Statistical Analyses

The distribution of baseline characteristics was calculated by the median MeDi score for the cohort (<5 versus ≥5), and was tested for differences using the Wilcoxon rank-sum test for continuous variables and the chi-squared test for categorical variables. The primary outcome was the change in eGFR from ≥60 ml/min per 1.73 m<sup>2</sup> at baseline to <60 ml/min per 1.73 m<sup>2</sup> at follow-up. Secondary outcomes included annualized eGFR change, as well as a

binary outcome for upper quartile of annualized eGFR decline within this cohort ( $\geq 2.5$  ml/min per  $1.73$  m<sup>2</sup> per year). The MeDi score was used continuously, dichotomized at the median score, and was also used as quartiles as distributed in the NOMAS cohort (0–3, 4, 5, and 6–9). Conditional logistic regression models that account for strata of time differences between the two measures of creatinine were fitted for the outcome of incident eGFR <60 ml/min per  $1.73$  m<sup>2</sup>, logistic regression modeling was used for the upper quartile of decline, and linear regression analyses were performed for the continuous annual change in eGFR outcome. Three models were fitted: (1) unadjusted, (2) adjusted for demographics, and (3) fully adjusted with comorbidities, medications, and laboratory results. Interaction terms between continuous MeDi scores and all covariates were tested for the primary outcome, with stratified analyses performed for interaction terms with a *P* value <0.05. All analyses were performed using SAS 9.3 software (Cary, NC).

## Results

### Baseline Characteristics

The sample size included 900 participants (Table 1), with a mean follow-up period of 6.9 years (SD 2.3 years) between serum creatinine measurements. The mean age was 64 years (SD 8.1 years); 65% of participants were Hispanic, 17% were black, and 15% were white. The mean baseline eGFR was 83.1 ml/min per  $1.73$  m<sup>2</sup> (SD 19.9 ml/min per  $1.73$  m<sup>2</sup>), with a mean annualized decline of 1.1 ml/min per  $1.73$  m<sup>2</sup> (SD 2.8 ml/min per  $1.73$  m<sup>2</sup>). The median MeDi score was 4 (interquartile range, 3–6). Participants with a MeDi

score  $\geq 5$  were more likely to be physically active compared with those with MeDi score <5 (*P*=0.003), but otherwise there were no statistically significant differences in characteristics between participants with a MeDi score  $\geq 5$  versus <5. We also assessed for differences in characteristics and risk factors between the 900 participants included in this study and the 191 individuals that were not included because of the unavailability of a MeDi score. We found that both groups were similar with respect to all variables, including annual change in eGFR, with the exception that the study group had a slightly lower HDL (45.7 versus 47.3 mg/dl).

### Primary Analyses

Table 2 represents the odds of incident eGFR <60 ml/min per  $1.73$  m<sup>2</sup>. Among those with an eGFR  $\geq 60$  at baseline (*n*=803), 115 participants (14%) developed eGFR <60 ml/min per  $1.73$  m<sup>2</sup>. In fully adjusted models, higher MeDi scores protected against kidney function decline. Every 1-point increase in the MeDi score was associated with a 17% reduced odds of the eGFR falling to <60 ml/min per  $1.73$  m<sup>2</sup> at follow-up (adjusted odds ratio [OR], 0.83; 95% confidence interval [95% CI], 0.71 to 0.96). In addition, a MeDi score  $\geq 5$  (versus <5) was associated with a 50% lower odds of incident eGFR <60 ml/min per  $1.73$  m<sup>2</sup> (adjusted OR, 0.50; 95% CI, 0.31 to 0.81). In fully adjusted analyses, associations with each of the upper two quartiles of MeDi scores did not reach statistical significance (Table 2). A sensitivity analysis excluding participants with incident eGFR <60 ml/min per  $1.73$  m<sup>2</sup> who had only small annual eGFR changes ( $\leq 1$  ml/min per  $1.73$  m<sup>2</sup> per year; *n*=10) yielded similar results (data not shown). Another sensitivity analysis excluded participants with an eGFR between

**Table 1. Baseline characteristics**

Characteristic	MeDi Score <5 ( <i>n</i> =455)	MeDi Score $\geq 5$ ( <i>n</i> =445)	<i>P</i> Value
Mean age, yr	64.2 (8.2)	64.1 (7.9)	0.58
Male sex	177 (39)	193 (43)	0.17
<b>Race/ethnicity</b>			
White	69 (15)	68 (15)	Ref
Black	83 (18)	74 (17)	0.67
Hispanic	291 (64)	295 (66)	0.88
Other	12 (3)	8 (2)	n/a
High school education	208 (46)	196 (44)	0.62
Medicare or private insurance	249 (55)	219 (49)	0.10
<b>Smoking status</b>			
Never	215 (47)	210 (47)	Ref
Past	163 (36)	172 (39)	0.60
Current	77 (17)	63 (14)	0.37
Physical activity (any exercise versus not)	232 (51)	270 (61)	0.003
ACE inhibitor or ARB usage	80 (18)	76 (17)	0.84
Hypertension	312 (69)	309 (69)	0.78
Diabetes	90 (20)	80 (18)	0.49
Mean BMI, kg/m <sup>2</sup>	28.2 (5.0)	27.8 (4.5)	0.37
Mean LDL, mg/dl	130.3 (34.5)	130.1 (34.5)	0.78
Mean HDL, mg/dl	45.6 (14.4)	45.8 (13.7)	0.75
Mean eGFR at baseline, ml/min per $1.73$ m <sup>2</sup>	82.4 (21.1)	83.9 (18.7)	0.06

Results are presented as *n* (%) or mean (SD). Baseline characteristics are for the entire study sample (*N*=900). For the primary outcome of incident eGFR <60 ml/min per  $1.73$  m<sup>2</sup>, 97 participants had an eGFR <60 ml/min per  $1.73$  m<sup>2</sup> at baseline and were excluded (*n*=803 for this analysis). ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; MeDi, Mediterranean Diet scoring system; Ref, reference; n/a, not applicable.

**Table 2.** Association between MeDi score and incident eGFR<60 ml/min per 1.73 m<sup>2</sup>

MeDi Score	OR (95% CI)	P Value
<b>Continuous (per 1-point increase in MeDi score)</b>		
Unadjusted	0.81 (0.72 to 0.92)	0.002
Demographic adjusted <sup>a</sup>	0.83 (0.73 to 0.95)	<0.01
Fully adjusted <sup>b</sup>	0.83 (0.71 to 0.96)	0.02
<b>MeDi score ≥5 (versus &lt;5)</b>		
Unadjusted	0.49 (0.33 to 0.75)	0.001
Demographic adjusted <sup>a</sup>	0.49 (0.32 to 0.75)	0.001
Fully adjusted <sup>b</sup>	0.50 (0.31 to 0.81)	0.004
<b>MeDi quartiles (unadjusted)</b>		
0–3	Ref	
4	1.30 (0.78 to 2.16)	0.31
5	0.52 (0.28 to 0.95)	0.03
6–9	0.60 (0.34 to 1.07)	0.08
<b>MeDi quartiles (demographic adjusted)</b>		
0–3	Ref	
4	1.44 (0.85 to 2.46)	0.18
5	0.50 (0.27 to 0.93)	0.03
6–9	0.67 (0.37 to 1.21)	0.18
<b>MeDi quartiles (fully adjusted)</b>		
0–3	Ref	
4	1.61 (0.88 to 2.97)	0.12
5	0.51 (0.26 to 1.02)	0.06
6–9	0.76 (0.39 to 1.46)	0.41

OR, odds ratio; 95% CI, 95% confidence interval.

<sup>a</sup>Adjusted for age (years), sex, race (black, white, Hispanic, or other), education (high school completion versus not), and insurance status (Medicare/private insurance versus Medicaid/no insurance).

<sup>b</sup>Adjusted for age (years), sex, race/ethnicity (black, white, Hispanic, or other), education (high school completion versus not), insurance status (Medicare/private insurance versus Medicaid/no insurance), physical activity (any exercise versus not), BMI (kg/m<sup>2</sup>), diabetes (yes or no), smoking status (never, past, or current), hypertension (yes or no), LDL (mg/dl), HDL (mg/dl), baseline eGFR (ml/min per 1.73 m<sup>2</sup>), and ACE inhibitor/ARB usage (yes or no).

60 and 69 ml/min per 1.73 m<sup>2</sup>, which also did not change results (data not shown).

### Secondary Analyses

We determined associations between MeDi scores and absolute changes in kidney function. We dichotomized the cohort at the upper quartile of annualized eGFR decline ( $\geq 2.5$  ml/min per 1.73 m<sup>2</sup> per year), which is higher than expected with normal aging. In fully adjusted analyses (Table 3), every 1-point increase in the MeDi score was associated with a 12% reduced odds of the eGFR declining  $\geq 2.5$  ml/min per 1.73 m<sup>2</sup> per year (OR, 0.88; 95% CI, 0.79 to 0.98). In fully adjusted analyses, associations with each of the upper two quartiles of MeDi scores either reached statistical significance or showed a strong trend (Table 3). With annualized eGFR change as the outcome, there was no statistically significant association in fully adjusted analysis with the continuous MeDi score (Table 4). By contrast, a trend for a reduced rate of decline in eGFR of 0.31 ml/min per 1.73 m<sup>2</sup> per year ( $P=0.06$ ) was found for participants with a MeDi score  $\geq 5$  versus  $<5$  in fully adjusted analysis.

These associations did not differ by baseline eGFR ( $\geq 60$  versus  $<60$  ml/min per 1.73 m<sup>2</sup>;  $P$  for interaction,  $P>0.05$ ), and these results were similar when only participants with a baseline eGFR  $\geq 60$  ml/min per 1.73 m<sup>2</sup> were considered (data not shown). Results were materially

unchanged if the CKD-EPI formula for estimating GFR was used (data not shown).

### Interactions between MeDi Scores and Other Risk Factors

There was an interaction between MeDi scores and diabetes for incident eGFR<60 ml/min per 1.73 m<sup>2</sup> ( $P$  for interaction,  $P=0.01$ ). Stratified analyses revealed that the Mediterranean diet may be more beneficial in non-diabetics. Every 1-point increase in MeDi score was associated with a 25% reduced odds of incident eGFR<60 ml/min per 1.73 m<sup>2</sup> (adjusted OR, 0.75; 95% CI, 0.63 to 0.89;  $P=0.001$ ) among non-diabetics, whereas there was no association among participants with diabetes (adjusted OR, 1.21; 95% CI, 0.87 to 1.69;  $P=0.25$ ). The effect of the MeDi score on incident eGFR<60 ml/min per 1.73 m<sup>2</sup> also differed by use of ACE inhibitor/ARB ( $P$  for interaction,  $P=0.04$ ). The MeDi score was associated with reduced odds of eGFR<60 ml/min per 1.73 m<sup>2</sup> at follow-up among those not taking these medications (adjusted OR per 1-unit increase in the MeDi score, 0.76; 95% CI, 0.63 to 0.90;  $P=0.002$ ), but not among those who were taking ACE inhibitors/ARBs (adjusted OR, 1.06; 95% CI, 0.80 to 1.39;  $P=0.69$ ).

### Analyses of Individual Components of the MeDi Score

Relationships between each MeDi component and the primary outcome were tested individually, and only vegetable intake associated with incident eGFR<60 ml/min per

**Table 3. Association between MeDi score and upper quartile of eGFR decline**

MeDi Score	OR (95% CI)	P Value
<b>Continuous (per 1-point increase in MeDi score)</b>		
Unadjusted	0.88 (0.80 to 0.96)	0.01
Demographic adjusted <sup>a</sup>	0.89 (0.80 to 0.98)	0.02
Fully adjusted <sup>b</sup>	0.88 (0.79 to 0.98)	0.02
<b>MeDi score <math>\geq 5</math> (versus <math>&lt;5</math>)</b>		
Unadjusted	0.65 (0.48 to 0.88)	0.01
Demographic adjusted <sup>a</sup>	0.65 (0.47 to 0.88)	0.01
Fully adjusted <sup>b</sup>	0.58 (0.41 to 0.83)	0.003
<b>MeDi quartiles (unadjusted)</b>		
0–3	Ref	
4	0.81 (0.53 to 1.23)	0.32
5	0.52 (0.33 to 0.82)	0.004
6–9	0.63 (0.41 to 0.95)	0.03
<b>MeDi quartiles (demographic adjusted)</b>		
0–3	Ref	
4	0.86 (0.55 to 1.33)	0.49
5	0.51 (0.32 to 0.81)	0.004
6–9	0.66 (0.43 to 1.02)	0.06
<b>MeDi quartiles (fully adjusted)</b>		
0–3	Ref	
4	1.01 (0.62 to 1.66)	0.96
5	0.49 (0.29 to 0.82)	0.01
6–9	0.67 (0.41 to 1.10)	0.11

<sup>a</sup>Adjusted for age (years), sex, race/ethnicity (black, white, Hispanic, or other), education (high school completion versus not), and insurance status (Medicare/private insurance versus Medicaid/no insurance).

<sup>b</sup>Adjusted for age (years), sex, race/ethnicity (black, white, Hispanic, other), education (high school completion versus not), insurance status (Medicare/private insurance versus Medicaid/no insurance), physical activity (any exercise versus not), BMI (kg/m<sup>2</sup>), diabetes (yes or no), smoking status (never, past, or current), hypertension (yes or no), LDL (mg/dl), HDL (mg/dl), baseline eGFR (ml/min per 1.73 m<sup>2</sup>), and ACE inhibitor/ARB usage (yes or no).

1.73 m<sup>2</sup> (adjusted OR, 0.59; 95% CI, 0.37 to 0.94) (Supplemental Table 1).

## Discussion

In this prospective, multiethnic cohort, we found that dietary patterns with increasing similarity to a Mediterranean diet were favorably associated with kidney function. For participants with a MeDi score at or above the median ( $\geq 5$ ), there was an approximate 50% decreased odds of developing incident eGFR  $<60$  ml/min per 1.73 m<sup>2</sup>. This is one of the few studies that has shown an association between a dietary pattern and reduced incidence of eGFR  $<60$  ml/min per 1.73 m<sup>2</sup> in participants with relatively preserved kidney function. The effect of the MeDi score on decline of eGFR also did not differ by baseline eGFR ( $\geq 60$  versus  $<60$  ml/min per 1.73 m<sup>2</sup>), raising the possibility that the effect of a Mediterranean diet may extend to those with prevalent CKD as well.

This study adds to the growing literature (observational studies and randomized control trials) demonstrating health benefits associated with Mediterranean-style diets (11–13). Prior studies examining Mediterranean-style diets and kidney function have been inconsistent, potentially because of important limitations that we attempted to address. Cross-sectional analyses have suggested a beneficial association with albuminuria, creatinine clearance, and

CKD (18–21). By contrast, reported outcomes from the Nurses' Health Study (NHS) and the Prevención con Dieta Mediterránea (PREDIMED) randomized clinical trial (which used the Mediterranean diet for primary prevention of cardiovascular disease) (12) differed from ours. In the NHS, there was an association between diet and eGFR decline; however, the benefit was significant for the Dietary Approaches to Stop Hypertension (DASH)-style diet and not for the prudent diet that was more similar to a Mediterranean diet (6). It is interesting to note that prudent and DASH diets were correlated ( $r=0.76$ ). Differences in outcomes between the NHS and our study may be due to differences in cohort composition and study design. For example, NHS participants were mainly older, white, and female, whereas NOMAS is a multiethnic cohort of men and women; food frequency questionnaires used in NHS and NOMAS differed; and NHS had repeated dietary assessments over time, which NOMAS did not. Finally, a secondary analysis of the PREDIMED trial at 1 year of follow-up did not show a significant difference in eGFR between the Mediterranean diet and control arms (22); however, the duration was nearly 6 years shorter than in the NOMAS cohort and may not have been long enough to determine an effect of diet on kidney function. There were also differences between the PREDIMED and NOMAS trials. PREDIMED had more men, a higher prevalence of diabetes, and a slightly lower baseline eGFR compared with

**Table 4. Association between MeDi score and annualized change in eGFR**

MeDi Score	Parameter Estimate (95% CI) <sup>a</sup>	P Value
<b>Continuous (per 1-point increase in MeDi score)</b>		
Unadjusted	0.13 (0.01 to 0.24)	0.03
Demographic adjusted <sup>b</sup>	0.09 (−0.02 to 0.21)	0.12
Fully adjusted <sup>c</sup>	0.07 (−0.03 to 0.17)	0.17
<b>MeDi score ≥5 (versus &lt;5)</b>		
Unadjusted	0.36 (−0.01 to 0.72)	0.06
Demographic adjusted <sup>b</sup>	0.31 (−0.05 to 0.67)	0.10
Fully adjusted <sup>c</sup>	0.31 (−0.01 to 0.64)	0.06
<b>MeDi quartiles (unadjusted)</b>		
0–3	Ref	
4	0.08 (−0.47 to 0.62)	0.79
5	0.30 (−0.25 to 0.85)	0.28
6–9	0.52 (−0.01 to 1.05)	0.05
<b>MeDi quartiles (demographic adjusted)</b>		
0–3	Ref	
4	−0.11 (−0.66 to 0.43)	0.68
5	0.25 (−0.29 to 0.80)	0.36
6–9	0.34 (−0.19 to 0.87)	0.21
<b>MeDi quartiles (fully adjusted)</b>		
0–3	Ref	
4	−0.37 (−0.86 to 0.12)	0.13
5	0.11 (−0.37 to 0.60)	0.65
6–9	0.20 (−0.28 to 0.67)	0.42

<sup>a</sup>Parameter estimate data are presented as the reduced rate of decline in eGFR in ml/min per 1.73 m<sup>2</sup> per year.

<sup>b</sup>Adjusted for age (years), sex, race/ethnicity (black, white, Hispanic, or other), education (high school completion versus not), and insurance status (Medicare/private insurance versus Medicaid/no insurance).

<sup>c</sup>Adjusted for age (years), sex, race/ethnicity (black, white, Hispanic, or other), education (high school completion versus not), insurance status (Medicare/private insurance versus Medicaid/no insurance), physical activity (any exercise versus not), BMI (kg/m<sup>2</sup>), diabetes (yes or no), smoking status (never, past, or current), hypertension (yes or no), LDL (mg/dl), HDL (mg/dl), baseline eGFR (ml/min per 1.73 m<sup>2</sup>), and ACE inhibitor/ARB usage (yes or no).

NOMAS. Moreover, the high percentage of Hispanics in NOMAS makes it difficult to directly compare the cohorts, because there are important race/ethnic differences in kidney disease progression.

There is biologic plausibility that a Mediterranean-style diet may protect against declining kidney function. One mechanism may be endothelial dysfunction, which has been associated with both CKD and cardiovascular risk, and has been favorably affected by a Mediterranean diet (16,31–33). Endothelial dysfunction is also closely linked to inflammation, which contributes to CKD. Recruitment of inflammatory cells into the kidney starts with their interaction with selectins found on endothelial cells, which were reduced with a Mediterranean diet in a controlled study in humans (31). Inflammatory biomarkers, lipid profile, and BP have all been favorably affected by a Mediterranean diet (as a whole or its components) in several randomized trials, which may also translate into beneficial kidney effects (32,34–38).

It is also possible that lower animal protein and red meat intake characteristic of this type of diet may benefit kidney function (39,40). Although meat consumption was not associated with incident eGFR < 60 ml/min per 1.73 m<sup>2</sup>, this study may have been inadequately powered to detect a relationship. The reduction of dietary red meat consumption may have led to increased vegetable consumption, which favorably affected kidney function in this study.

Similar findings have been reported elsewhere, with improvement in metabolic acidosis and phosphorus metabolism as possible mechanisms of action (41–43).

The benefit of MeDi was more apparent among non-diabetics and among those who did not take ACE inhibitors/ARBs. It is unclear why MeDi would preferentially benefit non-diabetics other than that any effect in participants with diabetes may be overwhelmed by other deleterious renal risk factors such as proteinuria. The lack of an effect among participants taking ACE inhibitors/ARBs may be due to the possibility that both MeDi and ACE inhibitors/ARBs could work through overlapping mechanisms such as lowering intraglomerular pressure or by decreasing inflammation. For instance, the amino acid profile associated with an animal protein diet (compared with a vegetable protein diet) has been associated with increased eGFR (44). Therefore, it is possible that the higher vegetable intake of a Mediterranean diet may exert beneficial effects through improved glomerular hemodynamics, which is a similar effect to that of ACEI/ARBs. In addition, 32% of participants with diabetes in this study were taking ACE inhibitors/ARBs (versus 14% of non-diabetics), which may also have diminished the Mediterranean diet benefit in participants with diabetes.

Ultimately, randomized trials are needed to confirm or refute the findings of these types of observational studies. Large-scale Mediterranean diet trials have successfully

been conducted in the general population (12,13). Although adherence to dietary interventions can vary, several trials have demonstrated that high compliance (even over several years) can be feasible (9,12,13). This could conceivably be extended to a CKD population, where numerous dietary trials involving protein restriction have been performed. Moreover, recent randomized trials involving high fruit and vegetable intake have shown safety and potential benefit in even advanced CKD, increasing the feasibility of a Mediterranean diet trial in this population (41,42).

Strengths of this study include the duration of follow-up, a well characterized cohort, a valid food frequency questionnaire, adjustment for multiple confounders, and multiethnic composition that permits generalizability of results. However, there are also limitations. First, the subgroup of participants within NOMAS who had follow-up creatinine values were likely healthier than the overall cohort, thus introducing a survival bias; this should, however, bias results toward the null. Second, there was no assessment of proteinuria. However, given that <20% of participants had diabetes, significant proteinuria would not be expected to be common. Third, only baseline food consumption data were available (which are limited because of self-reporting), and we could not adjust for dietary changes during follow-up. However, MeDi scores may not change significantly over time either. Analyses of the Washington Heights-Inwood Columbia Aging Project cohort, which was recruited from a geographic area similar to NOMAS, showed that MeDi scores remained relatively stable over 6–8 years of repeated measurement (29). Fourth, although we adjusted for physical activity, we cannot eliminate the possibility that the benefit seen with higher MeDi scores is related to an overall healthier lifestyle, as opposed to diet alone. Finally, we could not determine exactly how closely dietary patterns would need to resemble a true Mediterranean diet in order to potentially have beneficial kidney effects. Our categorical analyses showed a protective effect with MeDi scores  $\geq 5$ , and our continuous models demonstrated benefit with every 1-point increase in the MeDi score.

In conclusion, in a multiethnic cohort of men and women, we demonstrated that a Mediterranean-style diet was associated with lower risk of incident eGFR <60 ml/min per 1.73 m<sup>2</sup> and upper quartile of eGFR decline. If these data are confirmed in clinical trials, they will offer a novel and important approach in the fight against kidney disease. The growing body of literature suggesting that a Mediterranean-style diet has a kidney-protective effect supports the need for a randomized controlled trial in patients at risk for kidney disease and its progression.

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#### Disclosures

None.

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See related editorial, "Where What Is Not Stated or Required May Be the Most Illuminating," on pages 1826–1828.



**Supplemental Table 1: Association between individual components of MeDi and incident eGFR <60 mL/min/1.73m<sup>2</sup>**

	<b>Odds ratio (95% Confidence Interval)</b>	<b>p-value</b>
<b>High fruit intake</b>	<b>0.86 (0.54-1.38)</b>	<b>0.54</b>
<b>High cereal intake</b>	<b>0.74 (0.46-1.20)</b>	<b>0.22</b>
<b>High vegetable intake</b>	<b>0.59 (0.37-0.94)</b>	<b>0.03</b>
<b>High legume intake</b>	<b>0.74 (0.46-1.19)</b>	<b>0.21</b>
<b>High fish intake</b>	<b>1.00 (0.63-1.58)</b>	<b>0.99</b>
<b>Low meat intake</b>	<b>0.82 (0.52-1.29)</b>	<b>0.39</b>
<b>Low dairy intake</b>	<b>0.76 (0.48-1.21)</b>	<b>0.25</b>
<b>High monounsaturated:saturated fat ratio</b>	<b>0.98 (0.61-1.55)</b>	<b>0.92</b>
<b>Moderate alcohol consumption</b>	<b>0.94 (0.55-1.62)</b>	<b>0.83</b>

Adjusted for age (years), sex, race-ethnicity (black, white, Hispanic, other), education (high school completion vs not), insurance status (Medicare/private insurance vs Medicaid/no insurance), physical activity (any exercise vs not), body mass index (kg/m<sup>2</sup>), diabetes (yes/no), smoking status (never/past/current), hypertension (yes/no), low-density lipoprotein (mg/dL), high-density lipoprotein (mg/dL), baseline estimated glomerular filtration rate (mL/min/1.73m<sup>2</sup>), angiotensin converting enzyme inhibitor/angiotensin receptor blocker usage (yes/no)