Associations of Diet Quality and All-Cause Mortality Across Levels of Cardiometabolic Health and Disease

Vinke, Petra C; Navis, Gerjan; Kromhout, Daan; Corpeleijn, Eva

Published in:
Diabetes Care

DOI:
10.2337/dc20-2709

Publication date:
2021

Associations of Diet Quality and All-Cause Mortality Across Levels of Cardiometabolic Health and Disease: A 7.6-Year Prospective Analysis From the Dutch Lifelines Cohort

Petra C. Vinke,[1] Gerjan Navis,[2] Daan Kromhout,[1] and Eva Corpeleijn[1]

Diabetes Care 2021;44:1228–1235 | https://doi.org/10.2337/dc20-2709

OBJECTIVE

To simultaneously investigate the association of diet quality and all-cause mortality in groups with varying cardiometabolic diseases (CMDs) at baseline.

RESEARCH DESIGN AND METHODS

From the population-based Lifelines cohort, 40,892 non-underweight participants aged ≥50 years with data on diet quality and confounding factors were included (enrollment 2006–2013). From food-frequency questionnaire data, tertiles of the Lifelines Diet Score were calculated (T1 = poorest, T3 = best diet quality). Four CMD categories were defined: *1*) CMD free, *2*) type 2 diabetes, *3*) one cardiovascular disease (CVD), *4*) two or more CMDs. Months when deaths occurred were obtained from municipal registries up until November 2019. Multivariable Cox proportional hazards models were applied for the total population and stratified by CMD categories.

RESULTS

After a median follow-up of 7.6 years, 1,438 participants died. Diet quality and CMD categories were independently associated with all-cause mortality in crude and adjusted models ($P < 0.001$). A dose-response relationship of diet quality with all-cause mortality was observed in the total population ($P_{trend} < 0.001$, T2 vs. T3 = hazard ratio 1.22 [95% CI 1.07–1.41], T1 vs. T3 = 1.57 [1.37–1.80]). In stratified analyses, the association was significant for CMD-free individuals (T1 vs. T3 = 1.63 [1.38–1.93]) and for patients with type 2 diabetes (1.87 [1.17–3.00]) but not for patients with one CVD (1.39 [0.93–2.08]) or multiple CMDs (1.19 [0.80–1.76]).

CONCLUSIONS

A high-quality diet can potentially lower all-cause mortality risk in the majority of the aging population. Its effect may be greatest for CMD-free individuals and patients with type 2 diabetes. Tailored dietary guidelines may be required for patients with extensive histories of CMDs.

The Global Burden of Disease Study estimated that for all deaths that occurred worldwide in 2017, dietary risk was the leading behavioral risk factor, accounting

[1]Department of Epidemiology, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands
[2]Department of Nephrology, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands

Corresponding author: Petra C. Vinke, p.c.vinke@umcg.nl

Received 4 November 2020 and accepted 12 February 2021

This article contains supplementary material online at https://doi.org/10.2337/figshare.13964039.

This article is featured in a podcast available at https://www.diabetesjournals.org/content/diabetes-core-update-podcasts.

for 10.9 million deaths. Moreover, most of these deaths were induced by cardiometabolic diseases (CMDs), such as ischemic heart disease, stroke, and type 2 diabetes (1). However, the extent to which a high-quality diet can lower the mortality risks of groups with varying levels of existing cardiometabolic burden remains unclear.

Most prospective cohort studies on diet quality and mortality have investigated either disease-free populations or populations with specific disease diagnoses. Patients with histories of cancer, cardiovascular diseases (CVDs), or diabetes were excluded from most of the cohort studies examined in two meta-analyses that studied the association of diet quality and mortality risk (2,3). A recent meta-analysis on adherence to the Mediterranean diet and all-cause mortality only included prospective cohort studies conducted with healthy participants (4). Consequently, these meta-analyses obtained evidence of an association between healthy diets and mortality in study populations that were healthier than the general population. Other studies have specifically investigated associations of diet quality with mortality in participants with a history of CMDs. Two prospective cohort studies found that a high-quality diet was associated with lower risks (32% [5] and 27% [6] lower) of all-cause mortality in post–myocardial infarction patients. A third study found that patients with one of various CVDs had a 19% lower risk of all-cause mortality when better adhering to the Mediterranean diet (7). A meta-analysis of prospective diabetes cohorts found that adherence to a Mediterranean diet was associated with a 21% lower risk of CVD mortality (8). These findings indicate that a high-quality diet may lower mortality risks even when cardiometabolic health is impaired.

Few studies have simultaneously investigated the association of diet quality and mortality in subgroups of the population defined by existing cardiometabolic burden. Furthermore, whether a high-quality diet can lower mortality risks for populations with a history of multiple CMDs has not been determined. Therefore, the current study investigated the inverse association of diet quality and all-cause mortality within subgroups of the population-based Lifelines cohort, ranging from CMD-free participants to patients with multiple CMDs.

RESEARCH DESIGN AND METHODS

Cohort Design and Study Population

The Lifelines Cohort Study is a multidisciplinary prospective population-based cohort study examining, in a unique three-generation design, the health and health-related behaviors of 167,729 persons living in the North of the Netherlands. In Lifelines, a broad range of investigative procedures is used in assessment of the biomedical, sociodemographic, behavioral, physical, and psychological factors that contribute to health and disease of the general population, with a special focus on multimorbidity and complex genetics. The overall design and rationale of the study have previously been described in detail (9,10). Participants were included in the study between 2006 and 2013. Written informed consent was obtained from all participants. Lifelines is conducted in accordance with the Declaration of Helsinki and was approved by the Medical Ethics Committee of the University Medical Center Groningen under reference number 2007/152.

Adults aged 50 years or older were targeted in this study because in the Netherlands, the contribution of external causes of death, such as accidents or suicide, to overall mortality of adults $<$50 years exceeds that of CMDs (11). This left a total of 48,380 potential participants. Additionally, participants whose baseline data on diet quality or covariates were missing or unreliable, or who withdrew their consent, were excluded. Moreover, underweight participants and frail elderly (BMI $<$18.5 kg/m^2 for age $<$70 years, BMI $<$20 kg/m^2 for age $\geq$70 years) were excluded. For this group, dietary requirements may deviate from those of the general population, and mechanisms other than cardiometabolic health status may contribute to the increased mortality risk of this group. Of 48,380 Lifelines participants aged $\geq$50 years, 40,892 met the inclusion criteria (Supplementary Fig. 1).

Data Collection

Dietary Assessment

At baseline, diet over the previous month was assessed with a 110-item semiquantitative food-frequency questionnaire (FFQ) (12). Energy intake was estimated with the 2011 Dutch Food Composition Database (13). FFQ data were considered unreliable when the ratio between the reported energy intake and the basal metabolic rate, calculated with the Schofield equation (14), was $<$0.50 or $>$2.75 or when daily energy intakes for men and women were $<$800 kcal and 500 kcal, respectively (15).

The food-based Lifelines Diet Score (LLDS) was calculated as a measure of relative diet quality. This score is based on the scientific evidence on diet and chronic disease relations underlying the 2015 Dutch dietary guidelines (16). The development of the LLDS has previously been described (17). In brief, the LLDS ranks the relative intakes of nine food groups with proven positive health effects (vegetables, fruits, whole-grain products, legumes and nuts, fish, oils and soft margarines, unsweetened dairy products, coffee, and tea) and three food groups with proven negative health effects (red and processed meat, butter and hard margarines, and sugar-sweetened beverages). For each of these food groups, quintiles of consumption in g/1,000 kcal were determined and assigned 0–4 points. For negative food groups, higher scores were assigned for lower quintiles of consumption (Supplementary Table 1). The sum of these LLDS components varied between 0 and 48. For enabling comparability across studies, the quintiles for each food group were predefined within the total adult Lifelines cohort (N = 129,363). The scores were then categorized into tertiles within the current study population, with the third tertile indicating the highest diet quality.

Cardiometabolic Diseases and All-Cause Mortality

At baseline, participants were categorized according to the prevalence of CMDs (type 2 diabetes, chronic kidney disease [stages 3–5], myocardial infarction, angioplasty or bypass surgery, aortic aneurysm, heart or kidney transplantation, stroke, heart failure). These conditions were ascertained with use of questionnaires combined with data on prescribed medication and laboratory measurements (Supplementary Table 2). The following CMD categories were defined: *1*) CMD free; *2*) type 2 diabetes

without prevalent CVDs, as defined above; *3*) one CVD (referring to all of the included conditions other than type 2 diabetes); and *4*) two or more CMDs (any combination of two or more of the included conditions). These groups are mutually exclusive, meaning that each participant is categorized in only one of the groups. The Lifelines cohort was linked to municipal registries, which register all deaths of the municipalities' inhabitants. Participants were tracked passively, provided that they did not withdraw consent. Times of death (months and years) were collected up to November 2019. Data on the underlying causes of death were not available.

Demographics and Lifestyles

Participants' heights and body weights (without shoes and heavy clothing) were measured and rounded to 0.5 cm and 0.1 kg, respectively, for calculation of BMI (measured as weight in kilograms divided by the square of height in meters). Self-administered questionnaires at baseline were used to collect demographic data (ethnicity and educational levels) and lifestyles (alcohol consumption, smoking, and physical activity). Educational levels were categorized as low (International Standard Classification of Education [ISCED] levels 0–2: no education, primary school, lower vocational, or lower general secondary education), middle (ISCED levels 3–4: intermediate vocational training or higher secondary education), or high (ISCED levels 5–6: higher vocational or university education) (18). Energy intake (kilocalories per day) and alcohol consumption (grams per day) were estimated from the FFQ data (12). Participants were categorized as "never," "former," or "current" smokers. The validated Short QUestionnaire to ASsess Health-enhancing physical activity (SQUASH) was used for assessment of physical activity (19). Nonoccupational moderate-to-vigorous physical activity (MVPA), including sports, at moderate (4.0–6.4 METs) to vigorous (≥6.5 METs) intensity, was calculated in minutes per week. Missing MVPA data (n = 2,790 [6.8%]) were imputed with the hot-deck imputation macro for SPSS (20), which replaced a missing value with a value from another participant of the same sex with similar status for educational level, smoking, and energy intake.

Data Analysis

Cox proportional hazards regression analysis was performed for investigation of associations of diet quality and CMD categories with all-cause mortality. Participants' follow-up commenced at the month of their baseline assessment, and participants who were alive by November 2019 were censored at this time. The proportional hazards assumption was verified through inspection of the log − log plots. For the LLDS, tertile 3 was considered the reference group. For CMD categories, this was the group of CMD-free participants.

In the first analysis, independent associations of diet quality and CMD categories with all-cause mortality were investigated through the inclusion of both the LLDS in tertiles and the categorical CMD variable as independent variables in the model. The model was subsequently adjusted for potential confounders (sex, age, age squared, educational level, smoking status, energy intake, alcohol intake, and nonoccupational MVPA). Age squared was included because of the nonlinear association of age with mortality risk.

In the next phase, the association of diet quality and all-cause mortality was investigated stratified by CMD category, with adjustment for the same potential confounders noted above. To test whether the association of diet quality and all-cause mortality differed significantly among the four CMD categories, we included the interaction term of LLDS in tertiles and CMD categories in the unstratified model in which LLDS was coded as an ordinal variable. To test for a linear trend in the association of LLDS tertiles and mortality, we repeated both the main analysis and the stratified analyses after replacing the categorical LLDS tertile variable with a continuous variable containing the mean LLDS score for each tertile.

In the final Cox regression, the joint association of diet quality and CMD categories with all-cause mortality was investigated for comparison of mortality risks across strata of diet quality and CMDs simultaneously. Accordingly, a categorical variable with 12 levels that combined diet quality (LLDS tertiles) and the four CMD categories was included. CMD-free participants with a high-quality diet (tertile 3) were chosen as the reference group. The model was then adjusted for the potential confounders described above. The joint Cox regression was repeated in a sensitivity analysis, in which the category of CMD-free individuals was further divided into normal weight (BMI <25 kg/m^2), overweight (BMI 25–30 kg/m^2), and obese (BMI >30 kg/m^2) categories.

Analyses were performed with IBM SPSS, version 25 (Chicago, IL). Two-sided P levels <0.05 were considered statistically significant.

RESULTS

After a median follow-up of 7.6 years (interquartile range 6.8–8.6), 1,438 participants (852 men and 586 women) died. The average mortality rate was 4.6 per 1,000 person-years (6.2 for men and 3.3 for women). On average, CMD-free individuals had a 0.6-points-higher LLDS and were 7.3 years younger than patients with multiple CMDs (Table 1). The distribution of the LLDS across tertiles of the score was highly similar among the four CMD categories. Supplementary Table 3 shows the prevalence of different diseases among individuals with one CVD or multiple CMDs.

Diet Quality and Cardiometabolic Diseases Versus All-Cause Mortality

Diet quality and CMD categories were independently associated with all-cause mortality in the crude and adjusted models (P < 0.001) (Table 2). For diet, the mortality risk of individuals in the poorest LLDS tertile was 57% higher than for those in the tertile with the highest diet quality (T3) (hazard ratio [HR] 1.57 [95% CI 1.37–1.80], adjusted model). For CMD categories, the mortality risks for individuals with type 2 diabetes (1.44 [1.20–1.74]) or a single CVD (1.46 [1.23–1.74]) were similarly elevated in comparison with CMD-free individuals. For patients with multiple CMDs, mortality risk was approximately double that for CMD-free individuals (1.97 [1.66–2.35]). Kaplan-Meier curves are depicted in Supplementary Fig. 2.

Diet Quality and All-Cause Mortality Across Levels of Cardiometabolic Diseases

In the analyses stratified by CMD categories, diet quality was significantly associated with all-cause mortality in CMD-free individuals and in patients with type 2 diabetes (Table 3). The HR

Table 1—Baseline characteristics of the study population

	Total, $N = 40,892$	CMD category*			
		Free of CMD, $N = 35,298$	T2D, $N = 2,318$	1 CVD, $N = 1,912$	≥2 CMDs, $N = 1,364$
Sex (%)					
Male	44.0	42.0	49.8	54.2	71.4
Female	56.0	58.0	50.2	45.8	28.6
Age at baseline	59.1 ± 7.3	58.4 ± 6.9	61.8 ± 7.3	65.0 ± 8.2	65.7 ± 8.1
White, East/West European ethnicity (%)	99.1	99.2	97.9	99.4	98.7
Education level (%)					
Low	45.7	44.2	56.8	53.3	54.4
Middle	29.1	29.7	25.2	24.4	24.9
High	25.3	26.1	18.0	22.3	20.7
Mortality rate (per 1,000 person-years)					
Total	4.6	3.6	7.3	11.5	17.0
Male	6.2	4.6	9.5	15.1	17.7
Female	3.3	2.8	5.1	7.4	15.1
LLDS	26.1 ± 5.9	26.1 ± 5.9	25.9 ± 5.8	25.8 ± 5.7	25.5 ± 5.9
Energy intake (kcal/day)					
Male	2,206 ± 590	2,240 ± 594	2,073 ± 558	2,073 ± 545	1,991 ± 515
Female	1,766 ± 445	1,774 ± 445	1,701 ± 434	1,698 ± 427	1,660 ± 434
Smoking status (%)					
Never	34.7	35.6	31.4	30.4	24.0
Former	50.4	49.3	53.9	57.7	62.2
Current	14.9	15.1	14.7	11.9	13.8
Alcohol users (%)	83.3	84.5	72.8	79.2	76.8
Intake among users in g/day	6.8 (2.7–13.8)	6.8 (2.7–13.8)	6.4 (1.8–12.9)	6.8 (2.6–15.6)	6.7 (2.5–14.9)
Nonoccupational MVPA (min/week)	215 (80–420)	220 (90–420)	180 (60–390)	230 (70–420)	190 (60–390)
BMI (kg/m^2)					
Male	26.9 ± 3.4	26.7 ± 3.2	29.1 ± 4.1	27.3 ± 3.2	28.3 ± 3.7
Female	26.6 ± 4.4	26.3 ± 4.2	30.3 ± 5.4	27.6 ± 4.2	29.7 ± 5.1
Waist circumference (cm)					
Male	98.2 ± 10.0	97.3 ± 9.5	104.9 ± 11.3	99.7 ± 9.5	102.7 ± 10.6
Female	89.9 ± 11.6	89.0 ± 11.1	100.6 ± 12.7	92.8 ± 10.9	98.9 ± 13.3
SBP (mmHg)	131.0 ± 16.6	130.4 ± 16.4	137.2 ± 16.7	133.4 ± 17.6	132.7 ± 17.5
LDL cholesterol (mmol/L)	3.6 ± 0.9	3.6 ± 0.9	3.1 ± 1.0	3.2 ± 1.0	2.6 ± 0.9
HDL cholesterol (mmol/L)	1.6 ± 0.4	1.6 ± 0.4	1.3 ± 0.4	1.5 ± 0.4	1.3 ± 0.3
HbA_{1c} (%)	5.7 ± 0.5	5.6 ± 0.3	6.8 ± 0.9	5.7 ± 0.3	6.3 ± 0.8
HbA_{1c} (mmol/mol)	39.2 ± 5.3	38.2 ± 3.3	50.7 ± 10.1	39.2 ± 3.6	44.9 ± 9.2

Data are percentages, means ± SD, or median (25th–75th percentile). χ^2, one-way ANOVA or Kruskal-Wallis test depending on data characteristics was used for testing differences between CMD groups. P value <0.001 for all. SBP, systolic blood pressure; T2D, type 2 diabetes. *CMD categories are mutually exclusive; each participant is categorized in one group only.

for T1 vs. T3 was 1.63 (95% CI 1.38–1.93) for CMD-free individuals and 1.87 (1.17–3.00) for patients with type 2 diabetes. Among patients with one CVD (HR 1.39 [95% CI 0.93–2.08]) or multiple CMDs (1.19 [0.80–1.76]), the association of diet quality and all-cause mortality was nonsignificant. Statistically, the association of diet quality and all-cause mortality was not significantly modified by CMD categories (crude $P_{interaction} = 0.154$; adjusted $P_{interaction} = 0.255$).

In the joint analysis, the mortality risks related to diet within the CMD categories were compared with those for individuals who were CMD free and consumed a healthy diet (T3) (Fig. 1 and Supplementary Table 4). The mortality risk of patients with type 2 diabetes adhering to high-quality diets (T3) was slightly higher (HR 1.26 [95% CI 0.86–1.83]) than that of CMD-free individuals with a healthy diet. In patients with multiple CMDs, the mortality risk was at least double that of the reference group, irrespective of diet quality. In line with the stratified analyses, this joint analysis also showed that the difference in mortality risk between LLDS T1 and T3 was greatest for patients with type 2 diabetes and least pronounced for patients with multiple CMDs.

Diet quality and CMD categories were also jointly examined in a sensitivity analysis in which the category of CMD-free individuals was subdivided based on weight status (Supplementary Table 5). Mortality risks did not differ substantially among normal-weight, overweight, and obese CMD-free participants with varying levels of diet quality.

Table 2—Cox regression for investigation of the association of diet quality and CMD categories versus all-cause mortality during a median follow-up of 7.6 years

	Crude HR (95% CI)	Adjusted HR (95% CI)*
Tertile of LLDS		
T3 (Best diet quality)	1 (REF)	1 (REF)
T2	1.27 (1.11–1.46)	1.22 (1.07–1.41)
T1 (Poorest diet quality)	1.66 (1.46–1.89)	1.57 (1.37–1.80)
CMD categories#		
Free of CMD	1 (REF)	1 (REF)
T2D	2.04 (1.70–2.45)	1.44 (1.20–1.74)
1 CVD	3.27 (2.77–3.85)	1.46 (1.23–1.74)
≥2 CMDs	4.87 (4.14–5.74)	1.97 (1.66–2.35)

$N = 40{,}892$, $P < 0.001$ in crude and adjusted analyses. For LLDS tertile: $P_{trend} < 0.001$ in crude and adjusted analyses. REF, reference; T2D, type 2 diabetes. *LLDS tertile and CMD, adjusted for each other, education level, sex, age, age squared, smoking status, alcohol intake, nonoccupational MVPA, and energy intake. #CMD categories are mutually exclusive; each participant is categorized in one group only.

Adjustment for BMI or waist circumference led to minor attenuation of the results (Supplementary Table 6).

CONCLUSIONS

The findings of this large-scale prospective cohort study indicate that adherence to a healthy diet is associated with a lower all-cause mortality risk in individuals with varying cardiometabolic health levels. The most pronounced association of diet quality and all-cause mortality was observed among patients with type 2 diabetes. When these patients and CMD-free individuals adhered to a high-quality diet, the mortality risk of the former was only slightly elevated compared with that of the latter. The mortality risk was substantially higher for patients with multiple CMDs irrespective of diet quality. These results, in combination, show that improved diet quality can potentially lower all-cause mortality risk for most subgroups of the aging population. However, other strategies, including tailored dietary advice, may be needed for patients with complex and extensive histories of CMDs.

This study's findings confirm that poor diet quality is associated with a greater risk of all-cause mortality. Meta-analyses of prospective cohort studies that investigated other measures of overall diet quality, such as Mediterranean diet scores (3,21), Healthy Eating Index (22,23) or Dietary Approaches to Stop Hypertension (DASH) score (24,25), also found associations with all-cause or cause-specific mortality. For example, the pooled relative risk of all-cause mortality was 0.91 per 2-point improvement in the Mediterranean diet score (ranging from 0 to 7 or 9) (3). When the Alternate Healthy Eating Index and DASH score were applied, the pooled relative risk for all-cause mortality was 0.78 for the best versus poorest quantiles of the

Table 3—Cox regression for investigation of the association of diet quality and all-cause mortality during a median follow-up of 7.6 years, with stratification by CMD category

Baseline CMD category#	LLDS tertile	Crude HR (95% CI) and *P* values	Adjusted HR (95% CI) and *P* values*	N_{events} (%)	Mortality rate (cases/1,000 person-years)
Free of CMD	T3	1 (REF)	1 (REF)	258 (2.1)	3.0
	T2	1.24 (1.05–1.47)	1.21 (1.02–1.43)	302 (2.6)	3.0
	T1	1.69 (1.45–1.98)	1.63 (1.38–1.93)	415 (3.6)	4.6
		$P < 0.001$	**$P < 0.001$**		
		$P_{trend} < 0.001$	**$P_{trend} < 0.001$**		
T2D	*T3*	1 (REF)	1 (REF)	30 (3.8)	5.0
	T2	1.47 (0.92–2.35)	1.34 (0.83–2.17)	42 (5.6)	7.3
	T1	1.89 (1.22–2.95)	1.87 (1.17–3.00)	57 (7.2)	9.5
		$P = 0.018$	**$P = 0.028$**		
		$P_{trend} = 0.004$	**$P_{trend} = 0.008$**		
1 CVD	*T3*	1 (REF)	1 (REF)	42 (6.8)	9.1
	T2	1.32 (0.88–1.97)	1.28 (0.86–1.93)	55 (8.9)	11.9
	T1	1.46 (1.00–2.15)	1.39 (0.93–2.08)	68 (10.0)	13.3
		$P = 0.149$	$P = 0.265$		
		$P_{trend} = 0.056$	$P_{trend} = 0.117$		
≥2 CMDs	*T3*	1 (REF)	1 (REF)	47 (11.4)	15.7
	T2	1.12 (0.76–1.65)	1.11 (0.74–1.65)	55 (12.8)	17.5
	T1	1.12 (0.77–1.62)	1.19 (0.80–1.76)	67 (12.9)	17.5
		$P = 0.811$	$P = 0.695$		
		$P_{trend} = 0.571$	$P_{trend} = 0.396$		

REF, reference. *P* values <0.05 in boldface. *Adjustment for education level, sex, age, age squared, smoking status, alcohol intake, nonoccupational MVPA, and energy intake. #CMD categories are mutually exclusive; each participant is categorized in one group only.

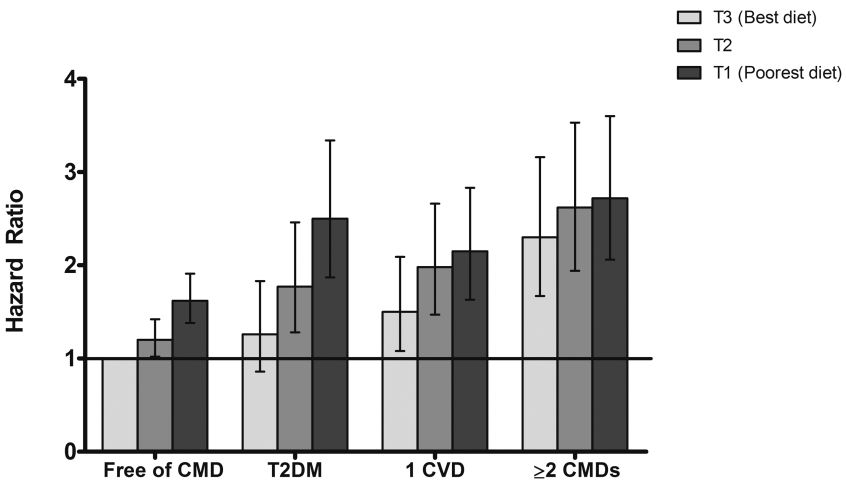

Figure 1—Illustration of the joint association of diet quality and CMD category with all-cause mortality risk. Results from adjusted Cox regression analyses, in which LLDS tertile 3 of the disease-free category is set as the reference group for all other groups. Data are HRs and 95% CIs. CMD categories are mutually exclusive; each participant is categorized in one group only.

scores (2). By comparison, the converted HR in the current study for the best versus poorest LLDS tertiles was 0.64. These findings foreground the importance of diet as a modifiable risk factor for mortality.

Our analyses, stratified by CMD categories, yielded further insights regarding the relevance of diet in subgroups of the aging population. Predictably, given the results of previous studies in which participants with CMDs were excluded (4), a significant association was observed for diet quality and mortality among CMD-free individuals. More importantly, our stratified analyses highlighted the considerable health potential of improved diet quality for patients with type 2 diabetes; the mortality risk was 87% greater when these patients' diet quality was poor. By contrast, a previous study found that an undisputed risk factor like smoking was associated with a 63% greater all-cause mortality risk in patients with type 2 diabetes without CVDs (26). This finding indicates that poor diet quality should be prioritized equally with smoking in risk factor management for patients with type 2 diabetes. It is hypothesized that the lower mortality risk for those patients adhering to a healthy diet will in part be established through a lower risk of CVD incidence in this at-risk patient population. Moreover, the results of our joint analysis showed that the mortality risk for patients with type 2 diabetes who adhered to a high-quality diet was only slightly higher than that for CMD-free individuals whose diet was equally healthy. Because intensive pharmaceutical treatment for type 2 diabetes is controversial, as it could increase mortality risk (27,28), dietary interventions may be a safe and efficacious alternative addition to standard pharmaceutical therapy. This foregrounds the importance of initiatives aimed at the implementation of lifestyle programs in the standard care of patients with type 2 diabetes (29,30).

The association between diet quality and mortality of patients with one CVD, though not significant, was of a meaningful magnitude. In the past, diet and lifestyle were emphasized solely for prevention of CVDs. However, the findings of more recent prospective cohort studies reveal that CVD patients who adhere to a healthy diet have a 19–32% lower all-cause mortality risk (5–7). The current study found a similar 28% lower all-cause mortality risk for patients with one CVD adhering to a healthy diet, although this result was not statistically significant. Together, these results indicate that dietary interventions have major health potential for preventing premature deaths of initially CMD-free individuals and of patients already suffering from CMDs.

A question that remains to be answered is whether an inverse association of diet quality and mortality exists when multiple CMDs are present. For this group, the 19% higher mortality risk for patients with a poor diet quality was not significantly different from risk in patients adhering to a healthy diet. Although a higher number of comorbidities is associated with an increased mortality risk (31,32), this does not explain why the risk would not be attenuated by a healthy diet. A possible explanation could be that the LLDS does not optimally reflect the dietary needs of elderly individuals with multiple CMDs. The LLDS is based on scientific evidence on the role of diet in the prevention of a number of major chronic diseases (16). The establishment of multimorbidity may entail altered nutritional needs, like a substantially elevated energy and protein requirement (33,34), which is not captured by the LLDS. Furthermore, as can be seen in Supplementary Table 3, the underlying profile of CVDs in the group with one CVD is qualitatively different from that in the group with two or more CMDs. For example, the prevalence of myocardial infarction and angioplasty or bypass surgery is much higher in the group with two or more CMDs, whereas chronic kidney disease is more prevalent in the group with one CVD. These different CVDs may differentially influence mortality risk and may also have different susceptibilities to dietary improvements. This may have affected both mortality risks and the association of diet and mortality in these groups. From a methodological perspective, the absence of a significant association in patients with one CVD or multiple CMDs could be related to a lack of power. However, in proportional hazards models, the power is determined by the number of events rather than by the number of censored observations (35). As the number of events was higher in the group with one CVD and the group with multiple CMDs than in the group with type 2 diabetes, this explanation becomes less plausible.

The strengths of this study include the large study population and the negligible dropout rate, as mortality data were collected passively from municipal registries. This results in a representative study population, which benefits the external validity of the study results. A limitation was that dietary data were self-reported and may have been prone to recall or reporter bias. Although the identification of CMDs relied on a combination of self-reporting, medication

use, and laboratory measurements, misclassification could have occurred. Additionally, since neither the incidence of new CMDs during follow-up nor the cause of death was taken into account, this study could not evaluate whether a decrease in CVDs is the mechanism underlying the lower mortality risks in disease-free individuals or patients with type 2 diabetes with higher diet quality. Furthermore, we did not have data on dates of diagnoses for the CMDs studied. Therefore, we could not rule out the potential confounding influence of disease duration on the association of diet and mortality risk. Finally, information on causes of death was not available; noncardiometabolic diseases could have contributed to mortality risks in the current study.

In conclusion, a healthy diet could beneficially influence all-cause mortality risks for individuals with and individuals without CMDs. Especially for patients with type 2 diabetes, diet quality stands out as a potential modifiable risk factor. Early lifestyle intervention in this patient population can lower mortality risk associated with this disease, presumably also by lowering the risk of concomitant CVDs. More research is needed to investigate the dietary needs of patients with one CVD and patients with multiple CMDs and to elucidate the influence of diet on mortality for these patients.

Acknowledgments. The Lifelines Biobank initiative has been made possible by subsidy from the Dutch Ministry of Health, Welfare and Sport; Dutch Ministry of Economic Affairs; University Medical Center Groningen; University of Groningen; and Northern Provinces of the Netherlands. The authors acknowledge the services of the Lifelines Cohort Study, the contributing research centers delivering data to Lifelines, and all study participants.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. P.C.V., G.N., D.K., and E.C. designed research. P.C.V. analyzed data. P.C.V., G.N., D.K., and E.C. wrote the manuscript. All authors read and approved the final manuscript. E.C. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. GBD 2017 Risk Factor Collaborators. Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017 [published correction appears in Lancet 2019;393:132; Lancet 2019;393:e44]. Lancet 2018;392:1923–1994
2. Schwingshackl L, Bogensberger B, Hoffmann G. Diet quality as assessed by the Healthy Eating Index, Alternate Healthy Eating Index, Dietary Approaches to Stop Hypertension Score, and health outcomes: an updated systematic review and meta-analysis of cohort studies. J Acad Nutr Diet 2018;118:74–100.e11
3. Sofi F, Macchi C, Abbate R, Gensini GF, Casini A. Mediterranean diet and health status: an updated meta-analysis and a proposal for a literature-based adherence score. Public Health Nutr 2014;17:2769–2782
4. Soltani S, Jayedi A, Shab-Bidar S, Becerra-Tomás N, Salas-Salvadó J. Adherence to the Mediterranean diet in relation to all-cause mortality: a systematic review and dose-response meta-analysis of prospective cohort studies. Adv Nutr 2019;10:1029–1039
5. Sijtsma FPC, Soedamah-Muthu SS, de Goede J, et al. Healthy eating and lower mortality risk in a large cohort of cardiac patients who received state-of-the-art drug treatment. Am J Clin Nutr 2015;102:1527–1533
6. Li S, Chiuve SE, Flint A, et al. Better diet quality and decreased mortality among myocardial infarction survivors. JAMA Intern Med 2013;173:1808–1818
7. Lopez-Garcia E, Rodriguez-Artalejo F, Li TY, et al. The Mediterranean-style dietary pattern and mortality among men and women with cardiovascular disease. Am J Clin Nutr 2014;99:172–180
8. Becerra-Tomás N, Blanco Mejía S, Viguiliouk E, et al. Mediterranean diet, cardiovascular disease and mortality in diabetes: a systematic review and meta-analysis of prospective cohort studies and randomized clinical trials. Crit Rev Food Sci Nutr 2020;60:1207–1227
9. Scholtens S, Smidt N, Swertz MA, et al. Cohort profile: lifeLines, a three-generation cohort study and biobank. Int J Epidemiol 2015;44:1172–1180
10. Stolk RP, Rosmalen JGM, Postma DS, et al. Universal risk factors for multifactorial diseases: LifeLines: a three-generation population-based study. Eur J Epidemiol 2008;23:67–74
11. Netherlands Central Bureau of Statistics. Overledenen; belangrijke doodsoorzaken (korte lijst), leeftijd, geslacht. Accessed 1 January 2019. Available from https://opendata.cbs.nl/statline/#/CBS/nl/dataset/7052_95/table?fromstatweb [in Dutch]
12. Siebelink E, Geelen A, de Vries JHM. Self-reported energy intake by FFQ compared with actual energy intake to maintain body weight in 516 adults. Br J Nutr 2011;106:274–281
13. RIVM/Dutch Nutrition Centre. NEVO-tabel Dutch Food Composition Table 2011, 2011
14. Schofield WN. Predicting basal metabolic rate, new standards and review of previous work. Hum Nutr Clin Nutr 1985;39(Suppl. 1):5–41
15. Willett W. Chapter 13: Issues in analysis and presentation of dietary data. In *Nutritional Epidemiology*, Oxford, U.K., Oxford University Press, 2012
16. Kromhout D, Spaaij CJK, de Goede J, Weggemans RM. The 2015 Dutch food-based dietary guidelines. Eur J Clin Nutr 2016;70:869–878
17. Vinke PC, Corpeleijn E, Dekker LH, Jacobs DR Jr., Navis G, Kromhout D. Development of the Food-Based Lifelines Diet Score (LLDS) and its application in 129,369 Lifelines participants [published correction appears in Eur J Clin Nutr 2019;73:1212]. Eur J Clin Nutr 2018;72:1111–1119
18. International Standard Classification of Education (ISCED) 1997. Accessed 8 May 2019. Available from http://uis.unesco.org/sites/default/files/documents/international-standard-classification-of-education-1997-en_0.pdf
19. Wendel-Vos GCW, Schuit AJ, Saris WHM, Kromhout D. Reproducibility and relative validity of the short questionnaire to assess health-enhancing physical activity. J Clin Epidemiol 2003;56:1163–1169
20. Myers TA. Goodbye, listwise deletion: presenting hot deck imputation as an easy and effective tool for handling missing data. Commun Methods Meas 2011;5:297–310
21. Trichopoulou A, Kouris-Blazos A, Wahlqvist ML, et al. Diet and overall survival in elderly people. BMJ 1995;311:1457–1460
22. Kennedy ET, Ohls J, Carlson S, Fleming K. The Healthy Eating Index: design and applications. J Am Diet Assoc 1995;95:1103–1108
23. Guenther PM, Casavale KO, Reedy J, et al. Update of the Healthy Eating Index: HEI-2010. J Acad Nutr Diet 2013;113:569–580
24. Dixon LB, Subar AF, Peters U, et al. Adherence to the USDA Food Guide, DASH Eating Plan, and Mediterranean dietary pattern reduces risk of colorectal adenoma. J Nutr 2007;137:2443–2450
25. Appel LJ, Moore TJ, Obarzanek E, et al.; DASH Collaborative Research Group. A clinical trial of the effects of dietary patterns on blood pressure. N Engl J Med 1997;336:1117–1124
26. Vazquez-Benitez G, Desai JR, Xu S, et al. Preventable major cardiovascular events associated with uncontrolled glucose, blood pressure, and lipids and active smoking in adults with diabetes with and without cardiovascular disease: a contemporary analysis. Diabetes Care 2015;38:905–912
27. Gerstein HC, Miller ME, Byington RP, et al.; Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 2008;358:2545–2559
28. Boussageon R, Bejan-Angoulvant T, Saadatian-Elahi M, et al. Effect of intensive glucose lowering treatment on all cause mortality, cardiovascular death, and microvascular events in type 2 diabetes: meta-analysis of randomised controlled trials. BMJ 2011;343:d4169
29. Delahanty LM, Levy DE, Chang Y, et al. Effectiveness of lifestyle intervention for type 2 diabetes in primary care: the REAL HEALTH-Diabetes randomized clinical trial. J Gen Intern Med 2020;35:2637–2646
30. Duijzer G, Haveman-Nies A, Jansen SC, et al. Effect and maintenance of the SLIMMER diabetes prevention lifestyle intervention in Dutch primary

healthcare: a randomised controlled trial. Nutr Diabetes 2017;7:e268
31. Di Angelantonio E, Kaptoge S, Wormser D, et al.; Emerging Risk Factors Collaboration. Association of cardiometabolic multimorbidity with mortality [published correction appears in JAMA 2015;314:1179]. JAMA 2015;314:52–60
32. Nunes BP, Flores TR, Mielke GI, Thumé E, Facchini LA. Multimorbidity and mortality in older adults: a systematic review and meta-analysis. Arch Gerontol Geriatr 2016;67:130–138
33. Richardson RA, Davidson HIM. Nutritional demands in acute and chronic illness. Proc Nutr Soc 2003;62:777–781
34. Phillips SM. Current concepts and unresolved questions in dietary protein requirements and supplements in adults. Front Nutr 2017;4:13
35. Hsieh FY, Lavori PW. Sample-size calculations for the Cox proportional hazards regression model with nonbinary covariates. Control Clin Trials 2000;21:552–560