Intake of Vegetables, Legumes, and Fruit, and Risk for All-Cause, Cardiovascular, and Cancer Mortality in a European Diabetic Population[1,2]

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Abstract

We examined the associations of intake of vegetables, legumes and fruit with all-cause and cause-specific mortality in a population with prevalent diabetes in Europe. A cohort of 10,449 participants with self-reported diabetes within the European Prospective Investigation into Cancer and Nutrition study was followed for a mean of 9 y. Intakes of vegetables, legumes, and fruit were assessed at baseline between 1992 and 2000 using validated country-specific questionnaires. A total of 1346 deaths occurred. Multivariate relative risks (RR) for all-cause mortality were estimated in Cox regression models and RR for cause-specific mortality were derived in a competing risk model. An increment in intake of total vegetables, legumes, and fruit of 80 g/d was associated with a RR of death from all causes of 0.94 [95% CI 0.90–0.98]. Analyzed separately, vegetables and legumes were associated with a significantly reduced risk, whereas nonsignificant inverse associations for fruit intake were

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observed. Cardiovascular disease (CVD) mortality and mortality due to non-CVD/non-cancer causes were significantly inversely associated with intake of total vegetables, legumes, and fruit (RR 0.88 [95% CI 0.81–0.95] and 0.90 [0.82–0.99], respectively) but not cancer mortality (1.08 [0.99–1.17]). Intake of vegetables, legumes, and fruit was associated with reduced risks of all-cause and CVD mortality in a diabetic population. The findings support the current state of evidence from general population studies that the protective potential of vegetable and fruit intake is larger for CVD than for cancer and suggest that diabetes patients may benefit from a diet high in vegetables and fruits.

Introduction

Dietary recommendations are an integral part in the treatment and management of diabetes mellitus (1), although data on their efficacy are limited (2). The objective of diabetes treatment is to reduce the risk of long-term vascular complications (3), predominantly cardiovascular diseases (CVD).[29] Increased risks of CVD (4,5) and a higher mortality rate than in the general population have been consistently found in diabetic populations (5,6). Recently, evidence for a higher risk of cancer at various sites has been reported to occur in diabetic compared with nondiabetic individuals (7–9).

Vegetable and fruit intakes have been extensively investigated as risk factors for cancer (10), CVD (11,12), or mortality (13–15) in the general population; however, data on associations between dietary behavior, including vegetables and fruit intake, and disease outcomes in diabetic populations are scarce (2). Therefore, we analyzed data from the European Prospective Investigation into Cancer and Nutrition (EPIC) study to examine the associations between intake of vegetables, legumes, and fruit, and risk for all-cause and cause-specific mortality in a population of diabetic individuals.

Subjects, Materials, and Methods

EPIC is an ongoing multicenter prospective cohort study designed to investigate associations between diet and other lifestyle behaviors with chronic diseases, especially cancer. A detailed description of the study design and methods used can be found elsewhere (16). In brief, between 1992 and 2000, >500,000 study participants were recruited in 23 study centers located in 10 European countries to be followed for cancer incidence and cause-specific mortality. Participants ranging from 35 to 70 y were recruited in study centers in France, Germany, Greece, Italy, The Netherlands, Spain, United Kingdom, Sweden, Denmark, and Norway. Study populations were population-based samples from designated geographic areas (e.g. town or province), with the exceptions of France (members of the health insurance for state school employees), subsamples of the Italian and Spanish cohort (blood donors), Utrecht (The Netherlands), Florence (Italy; women invited for breast cancer screening), and a subsample in Oxford (health-conscious group, vegetarians). Individuals signed informed consent forms, after which self-administered diet and lifestyle questionnaires were mailed to the participants. In the Spanish centers, Ragusa, Naples, and Greece, interviewer-administered questionnaires were used. All participants were invited to a study center for an examination that included anthropometric and blood pressure measurements. Approval for this study was obtained from the ethical review boards of the International Agency for Research on Cancer and from all local institutions where subjects had been recruited for the EPIC study.

Study population. The study population for this study was the group of participants in the EPIC cohort reporting a diagnosis of diabetes mellitus at baseline ($n = 13{,}838$). After exclusion of diabetic participants missing dietary questionnaire information ($n = 144$) or date of death ($n = 3$) or with implausible energy intake (top or bottom 1% of the ratio of energy intake:energy requirement; $n = 437$), a total of 13,254 participants with self-reported diabetes mellitus were identified. Of this population, 1718 participants missing information on age at diabetes diagnosis that included the cohorts from Norway and Umea (Sweden) and 1087 participants without information on waist-to-hip ratio were excluded. A total of 10,449 participants with self-reported diabetes mellitus were identified for this analysis.

Dietary assessment. Dietary intake during the previous 12 mo was assessed at baseline by means of country-specific instruments that had been developed and validated in a series of studies within the various source populations (17). Extensive quantitative dietary questionnaires with up to 300–350 food items were used in Italy, The Netherlands, Germany, Greece, France, and Spain. Semiquantitative questionnaires were used in Denmark and Naples. Combined dietary methods of food records and questionnaires were used in the UK and Malmö (16).

In addition, a highly standardized reference dietary measurement was taken from an 8% age-stratified random sample of the cohort using a computerized 24-h dietary recall (18,19).

To evaluate associations between fruit and vegetable consumption and mortality risk, total vegetables, legumes, and fruit intake were considered separately and combined. Soy products were included in the legumes food group. Furthermore, vegetable subgroups were analyzed: fruiting, root (not including potatoes), leafy vegetables, cabbages, mushrooms, and garlic/onion vegetables. A detailed description of the food groups and their consumption in the EPIC study has been described in (20).

Assessment of anthropometric and lifestyle exposure. In all EPIC centers, except for Oxford and France, height, weight, and waist and hip circumference were measured on all subjects using similar protocols. In Oxford, measurements were available only for a restricted number of participants, but self-reported weight, height, and waist and hip circumference were obtained from all individuals. Gender- and age-specific anthropometric values were predicted from subjects with measured and self-reported body measures using linear regression models as described previously (21). For France, only participants with measured waist and hip circumferences were included.

Further lifestyle- and health-related variables were collected using nondietary questionnaires. These included questions on smoking history, education, occupational history, physical activity, and medical history, including diabetes mellitus, heart attack, cancer, hypertension, and hyperlipidemia. In most centers, the assessment of physical activity covered core questions about recreational physical activities (cycling, walking, gardening, sports) and household activities (housekeeping and do-it-yourself) (22). Variables were assigned metabolic equivalent task-h/wk and metabolic equivalent task scores were calculated. Furthermore, diabetic participants were asked whether or not they used insulin.

Outcome ascertainment. Causes and dates of deaths were ascertained using record linkages with local, regional, or central cancer registries, boards of health, death indexes (Denmark, Italy, the Netherlands, Spain, the United Kingdom), or by active follow-up (Germany, Greece, France). France, Germany, and Greece identified deceased subjects with follow-up mailings and subsequent inquiries to municipality registries, regional health departments, physicians, or hospitals. Participants were followed from study entry until death, emigration, withdrawal, or end of follow-up period. Mortality data were coded following the rules of the 10th revision of the

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[29] Abbreviations used: CVD, cardiovascular disease; EPIC, European Prospective Investigation into Cancer and Nutrition; ICD-10, 10th revision of the International Statistical Classification of Diseases, Injuries and Causes of Death; RR, relative risk.

International Statistical Classification of Diseases, Injuries and Causes of Death (ICD-10), where the underlying cause is the official cause of death. On March 1, 2007, 1346 deaths had been registered among 10,449 diabetic EPIC participants. For the cause-specific analysis, death due to circulatory diseases as CVD (ICD-10 I00-I99; $n = 517$), death due to cancer (ICD-10 C00-C97; $n = 319$), and death due to all other specified causes were grouped ($n = 323$); 187 of deceased diabetic participants for whom no information on the specific cause of death was available were excluded from the cause-specific analysis but were included in the analysis for total mortality.

Statistical analysis. Food intakes were analyzed as predicted by regression calibration. Dietary intakes for the total cohort were calibrated using a fixed effects linear model in which gender- and center-specific 24-h dietary recall data were regressed on the questionnaire data controlling for covariates (weight, height, age, and season of administration of dietary questionnaires). A set of weights was used to model the effect of season and the day (weekdays vs. weekend days) when the 24-h recall was obtained. Zero consumption values in the dietary questionnaire were excluded from the regression calibration models and kept as 0 values. Single values negative after the calibration procedure were set to 0 as well. Details of the calibration procedure and its rationale can be found in (23,24).

For the analysis of all-cause mortality, hazard rate ratios were estimated as relative risks (RR) using Cox proportional hazard models with center and age at enrolment in 1-y categories as stratum variables to control for differences in questionnaire design, follow-up procedures, and other nonmeasured center effects, and to be more robust against violation of the proportionality assumption. Age was used as the primary time variable with entry time defined as the subject's age in days at recruitment and exit time defined as the subject's age in days at death or censoring (lost to follow-up or end of follow-up period). Participants have been followed for 9 y with a range of <1 to >14 y. Hazard rate ratios of specific causes of death estimated as RR were derived from a competing risk model (25,26) with CI derived from robust estimates of the covariance matrix (27). This method is adequate when the exposure is investigated in relation to multiple outcomes simultaneously. In this model, RR estimates were mutually controlled for the association of vegetable, legume, or fruit intake with all other outcomes.

Multivariate regression models were adjusted for sex; smoking status defined as never, former (quit >10 y ago; ≤10 y ago, or unknown), current

TABLE 1 Baseline characteristics of participants with self-reported diabetes[1]

	Quartile of fruit, vegetables, and legumes intake[2]			
Characteristic	1	2	3	4
n	2612	2612	2613	2612
Men, *%*	59	36	36	53
Age, *y*	57 ± 8	59 ± 9	59 ± 9	56 ± 8
Age at diabetes diagnosis, *y*	47 ± 13	49 ± 13	50 ± 12	48 ± 11
BMI, *kg/m²*	28.3 ± 4.9	28.8 ± 5.3	29.0 ± 5.1	29.1 ± 4.7
Waist-to-hip ratio	0.93 ± 0.09	0.90 ± 0.09	0.90 ± 0.09	0.91 ± 0.09
Insulin treatment, *%*				
Yes	32	20	17	16
No	51	61	67	73
Unknown	18	19	16	11
Heart attack, *%*				
Yes	9	6	5	4
No	79	87	91	94
Cancer, *%*				
Yes	5	4	3	1
No	78	86	90	95
Hypertension, *%*				
Yes	35	45	45	40
No	33	41	49	57
Hyperlipidemia, *%*				
Yes	27	38	39	42
No	41	50	54	54
Smoking status, *%*				
Never	34	52	55	51
Former, >10 y	26	21	18	15
Former, ≤10 y	13	10	10	13
Current, <20 cigarettes/d	15	10	9	13
Current, ≥20 cigarettes/d	12	7	7	7
Unknown	0	1	1	1
Physical activity, *%*				
Inactive	16	11	10	14
Moderately inactive	36	31	29	28
Moderately active	40	51	54	50
Active	6	7	6	8
Missing	2	1	0	0
Energy intake, *kJ/d*	8816 ± 1749	7987 ± 1887	7945 ± 1669	9096 ± 1992

[1] Values are percentages or mean ± SD; $n = 10{,}449$.

[2] Differences across quartiles were tested with the chi-square test for categorical variables and with the *t* test for slope in linear regression models of mean values on intake of fruit, vegetables, and legumes for continuous variables. $P < 0.01$ for all variables. Due to the large sample size, all tests were significant, so all variables differed.

TABLE 2 RR [95% CI] for intake of vegetables, legumes, and fruit, and all-cause mortality in a diabetic population[1]

	Quartiles of food intake					
Food group	1	2	3	4	*P*-trend	Continuous exposure[2]
Vegetables, legumes, and fruit						
Median intake, *g/d*	283	390	474	630		
Cases/person-years	478/ 3,890	315/22,065	326/22,399	227/25,174		
Sex, age, energy-adjusted RR [95% CI]	1	0.73 [0.62–0.87]	0.79 [0.66–0.95]	0.75 [0.59–0.94]	0.02	0.93 [0.89–0.97]
Multivariate adjusted RR [95% CI]	1	0.75 [0.63–0.89]	0.80 [0.66–0.97]	0.76 [0.60–0.96]	0.03	0.94 [0.90–0.98]
Vegetables						
Median intake, *g/d*	127	164	198	259		
Cases/person-years	432/24,028	333/22,839	271/22,933	310/23,730		
Sex, age, energy-adjusted RR [95% CI]	1	0.86 [0.73–1.01]	0.73 [0.60–0.88]	0.81 [0.65–1.01]	0.05	0.88 [0.79–0.99]
Multivariate adjusted RR [95% CI]	1	0.91 [0.77–1.07]	0.76 [0.62–0.92]	0.78 [0.63–0.98]	0.03	0.87 [0.77–0.97]
Legumes						
Median intake, *g/d*	0	5	17	32		
Cases/person-years	450/24,442	301/22,581	280/22,768	315/23,737		
Sex, age, energy-adjusted RR [95% CI]	1	0.91 [0.77–1.08]	0.84 [0.66–1.06]	0.73 [0.56–0.95]	0.02	0.92 [0.85–1.00]
Multivariate adjusted RR [95% CI]	1	0.95 [0.80–1.14]	0.85 [0.66–1.08]	0.72 [0.55–0.95]	0.02	0.93 [0.86–1.01]
Fruit						
Median intake, *g/d*	130	195	262	379		
Cases/person-years	477/23,360	351/22,098	291/22,860	227/25,210		
Sex, age, energy-adjusted RR [95% CI]	1	0.80 [0.68–0.94]	0.83 [0.70–0.99]	0.85 [0.68–1.05]	0.14	0.94 [0.89–0.99]
Multivariate adjusted RR [95% CI]	1	0.83 [0.71–0.98]	0.88 [0.74–1.05]	0.91 [0.73–1.12]	0.42	0.95 [0.90–1.01]

[1] $n = 10{,}449$; all models are stratified on age and study center, and adjusted for sex, smoking status (never, former < 10 y, former > =10 y, current <20 cigarettes, current > = 20 cigarettes, unknown), self-reported heart attack at baseline (yes, no/unknown), self-reported hypertension at baseline (yes, no/unknown), self-reported cancer at baseline (yes, no/unknown), WHR (continuous), insulin treatment (yes, no/unknown), age at diabetes diagnosis (continuous), energy intake (continuous), alcohol intake (continuous).

[2] Total of 80 g/d for vegetables, legumes, and fruit; vegetables; fruit; 20 g/d for legumes.

(<20, or unknown; ≥20 cigarettes smoked per day); self-reported heart attack, hypertension, or cancer at baseline (yes, no/unknown); waist-to-hip ratio (continuous); insulin treatment (yes, no/unknown); age at diabetes diagnosis (continuous); energy intake (continuous); and alcohol intake (continuous). To examine if associations for intake of total vegetables, legumes, and fruit differ between individuals who are at different mortality risk per se, potential interactions with sex, smoking status, age at diabetes diagnosis, or waist-to-hip ratio were analyzed with the respective interaction terms in regression models. As a further sensitivity analysis, we restricted the study population to participants ≥60 y of age.

RR were estimated for quartiles of vegetables, legumes, and fruit intakes based on the distribution of intakes in diabetic participants. As a test for trend, median values for quartiles were analyzed as continuous variables in the respective regression models. Models were also fit on a continuous scale. Additionally, restricted cubic spline regression (28,29) was used to examine nonlinearity of the RR functions.

All statistical tests were 2-tailed and $P < 0.05$ was considered significant. Analyses were performed using SAS 9.1 (SAS Institute).

Results

Mean age at baseline ranged from 56 to 59 y across quartiles of vegetable, legume, and fruit intake, not showing a trend (**Table 1**). The percentage of diabetic participants treated with insulin was inversely associated with intake of vegetables, legumes, and fruit, ranging from 32% in the lowest quartile to 16% in the highest. The percentage of diabetics with a self-reported heart attack at baseline was also inversely associated with intake of total vegetables, legumes, and fruit. There was a positive association with self-reported absence of hypertension at baseline and hyperlipidemia with vegetable, legume, and fruit intake. A total of 1346 deaths occurred, 517 due to circulatory diseases, 319 due to cancer, and 323 due to other specified causes.

Intake of total vegetables, legumes, and fruit was inversely associated with risk for all-cause mortality (**Table 2**). An increment in intake by 80 g/d was associated with a significant risk reduction of 6% ([RR 0.94 [95% CI 0.90–0.98]). The respective RR were 0.95 [0.89–1.00] for men and 0.93 [0.85–1.03] for women. Analyzed separately, intakes of vegetables and legumes were also inversely associated with risk for all-cause mortality (Table 2). Associations for total fruit intake were inverse but did not reach significance in the multivariate model ($P = 0.42$). In a model including vegetables, legumes, and fruit as separate variables, RR were below 1, with a significant RR for vegetables (data not shown). Additional adjustment for physical activity (inactive, moderately inactive, moderately active, active, missing), self-reported hyperlipidemia, or educational attainment changed RR estimates only marginally (data not shown). Adjustment for actual measured blood pressure, which was available for approximately two-thirds of the diabetic population, did not lead to different conclusions (data not shown). RR were essentially the same when we replaced waist-to-hip ratio with waist-to-height ratio, BMI, or waist circumference in multivariate models (data not shown). No evidence for nonlinear associations was found for any of the food group variables (data not shown). Sex, smoking status, age at diagnosis, and waist-to-hip ratio did not modify the associations between intake of fruits and vegetables and mortality risk (data not shown). Associations among participants ≥ 60 y of age ($n = 4591$) were similar to results for the overall group and reached significance for legumes only (data not shown). To confirm our findings, we calculated a multivariate-adjusted regression model with observed intake of total vegetables, legumes, and fruit, i.e. without regression calibration. For the fully adjusted model, RR [95% CI] were 0.83 [0.71–0.99] for the 2nd quartile compared with the lowest, 0.75 [0.62–0.90] for the 3rd quartile, and 0.78 [0.62–0.97] for the highest quartile (P-trend = 0.046).

For sensitivity analyses, we restricted our population to those individuals with a diabetes diagnosis at age 40 or older ($n =$

8408). By doing so, we aimed at excluding all type 1 diabetes patients. RR for intake of total vegetables, legumes, and fruit was 0.95 [95% CI 0.90–1.00] ($P = 0.041$) for an increment of 80 g/d, which was essentially the same as for the overall group. Associations for participants reporting insulin treatment ($n = 2197$) or no insulin treatment ($n = 6555$) were different ($P < 0.0001$), with a stronger effect in those not treated with insulin (RR 0.90 [95% CI 0.84–0.96]) compared with those treated with insulin (RR 0.96 [95% CI 0.87–1.06]).

Analyses of vegetable subgroups showed intake of root vegetables was associated with a significantly decreased RR (0.91 [95% CI 0.84–0.99]) for an increase in intake of 20 g/d (**Table 3**). Associations for the remaining vegetable subgroups, except mushrooms, were inverse but not significant (Table 3).

The results for cause of death-specific analyses (**Table 4**) suggested that intake of total vegetables, legumes, and fruit was inversely associated with CVD mortality and mortality due to other causes but not with cancer mortality. Differences in RR for CVD mortality or mortality due to non-CVD/non-cancer causes compared with the RR risk for cancer mortality were significant. Associations for CVD mortality were inverse for all dietary exposure variables. RR were essentially unchanged when participants with prevalent heart attack were excluded from the analysis (data not shown). No significant associations of any dietary exposure variable with cancer mortality was observed. All RR were close to unity.

Discussion

In this study, a significant inverse association existed between intake of total vegetables, legumes, and fruit and all-cause mortality in a European diabetic population. Associations were inverse for deaths due to CVD and non-CVD/non-cancer causes, but not for deaths due to cancer.

To our knowledge, only 3 prospective studies investigated food intakes as risk factors for disease incidence or mortality in diabetic populations to date (30–32) and only one of those evaluated vegetables, legumes, and fruit (32). In that study, overall mortality and cardiovascular mortality was investigated in the Greek arm of the EPIC study, analyzing data of a subgroup of 1013 participants who took drugs for diabetes mellitus and did not report any comorbidities at enrollment (32). Estimated RR for total mortality and vegetables (1.10 [95% CI 0.80–1.51]), legumes and potatoes (0.85 [95% CI 0.63–1.13]), and fruits and nuts (0.93 [95% CI 0.69–1.26]) were not significant. The associations between vegetables and fruit intake and CVD and cancer have been extensively investigated in the general population and have been found to be inverse for CVD (11,12,33–36). Findings for cancer were less consistent (10,33).

TABLE 3 RR [95% CI] for intake of subtypes of vegetables, and all-cause mortality in a diabetic population[1]

Vegetable subtype	RR [95% CI]
Fruiting vegetables (40 g/d)	0.92 [0.84–1.02]
Root vegetables (20 g/d)	0.91 [0.84–0.99]
Leafy vegetables (8 g/d)	0.97 [0.92–1.03]
Cabbages (8 g/d)	0.99 [0.94–1.04]
Mushrooms (1 g/d)	1.01 [0.99–1.03]
Garlic/onion vegetables (8 g/d)	0.97 [0.87–1.10]

[1] $n = 10{,}449$; all models are stratified on age and study center, and adjusted for sex, smoking status (never, former <10 y, former ≥10 y, current <20 cigarettes/d, current ≥20 cigarettes/d, unknown), self-reported heart attack at baseline (yes, no/unknown), self-reported hypertension at baseline (yes, no/unknown), self-reported cancer at baseline (yes, no/unknown), waist-to-hip ratio (continuous), insulin treatment (yes, no/unknown), age at diabetes diagnosis (continuous), energy intake (continuous), alcohol intake (continuous).

Of note, inverse associations seemed to be stronger for vegetables and legumes than for fruit intake in the regression models for all-cause mortality and cause-specific mortality, suggesting that consumption of vegetables and legumes is more beneficial for diabetes patients than consumption of fruit.

Our findings seem plausible, because type 2 diabetes often is associated with overweight or obesity. Modest weight loss has been shown to improve insulin sensitivity and reduces the CVD risk factors associated with type 2 diabetes (37–39). A diet high in vegetables, legumes, and fruit might help diabetic patients lose weight (39). However, numerous possible mechanisms explaining the effect of fruits and vegetables on health outcomes have been discussed, e.g. the antioxidative effects of vitamins, minerals, or polyphenols, a homocysteine-reducing effect of folate and B vitamins, or the enhancement of detoxification enzymes (12,40).

The question arises whether amounts of vegetables and legumes consumed by diabetic men and women differ from those consumed by the nondiabetic population. A comparison of intakes assessed in the EPIC study showed that vegetable and legume intakes, as well as intake of fruit, were slightly higher in the diabetic than the nondiabetic population (data not shown). However, different studies have reported that the majority of adults with type 2 diabetes did not follow guidelines for fruit and

TABLE 4 RR [95% CI] for fruit, vegetables, and legumes intake, and cause-specific mortality in a diabetic population[1]

	Cause of death			*P* for differences		
Food group	CVD[2]	Cancer[3]	Other causes[4]	CVD vs. cancer	CVD vs. other	Cancer vs. other
Vegetables, legumes, and fruit (80 g/d)	0.88 [0.81–0.95]	1.08 [0.99–1.17]	0.90 [0.82–0.99]	<0.01	0.67	<0.01
Vegetables (80 g/d)	0.85 [0.68–1.07]	1.09 [0.87–1.36]	0.72 [0.57–0.91]	0.13	0.32	0.01
Legumes (20 g/d)	0.72 [0.60–0.88]	1.09 [0.96–1.24]	1.02 [0.93–1.12]	<0.01	<0.01	0.41
Fruit (80 g/d)	0.90 [0.81–0.99]	1.08 [0.98–1.19]	0.92 [0.82–1.03]	<0.01	0.72	0.04

[1] $n = 10{,}262$; all models are stratified on age and study center, and adjusted for sex, smoking status (never, former <10 y, former ≥10 y, current <20 cigarettes/d, current ≥20 cigarettes/d, unknown), self-reported heart attack at baseline (yes, no/unknown), self-reported cancer at baseline (yes, no/unknown), self-reported hypertension at baseline (yes, no/unknown), WHR (continuous), insulin treatment (yes, no/unknown), age at diabetes diagnosis (continuous), energy intake (continuous), alcohol intake (continuous).

[2] ICD-10 codes I00–99; $n = 517$.

[3] ICD-10 codes C00–97; $n = 319$.

[4] $n = 323$.

vegetable consumption (41) and healthy foods might be overreported, because dietary energy intake has been shown to be underreported in obese diabetic patients (42). Although this type of misreporting would not be of concern for risk assessments within the diabetic population, absolute intakes as reported in our study should be interpreted cautiously.

Our study has several limitations. First is its reliance on self-reports of diabetes. However, in a different setting, a comparison between self-reports and medical records in a group of elderly men in the US has shown that concordance was excellent for diabetes ($\kappa = 0.84$) and substantial for hypertension ($\kappa = 0.70$) (43). Other studies in the US and Canada reported similar κ (44,45). Second, we were unable to distinguish between type 1 and 2 diabetes diagnoses. However, our sensitivity analysis using data of those individuals diagnosed at or after 40 y old showed the same inverse association as in the overall cohort. Third, we were unable to adjust for use of oral hypoglycemic medication and information on use of insulin was not available for all participants. We also lacked information about if and what kind of advice about diet diabetes patients might have received. Those participants reporting higher vegetable and fruit intake might comply better with other dietary and lifestyle recommendations and treatment, which could have affected the course of their diabetes. Fourth, information on prevalent heart attacks, hypertension, and cancer, which we adjusted for in our analysis, were also self-reported at baseline and the percentage of unknown conditions was higher for participants with low intake of fruit, vegetables, and legumes. We therefore cannot rule out residual confounding. However, substitution of self-reported hypertension by blood pressure measurement, which was available for about two-thirds of the diabetic population, did not change our conclusions. Also, after excluding participants with unknown status of prevalent heart attacks, hypertension, or cancer, the association with total vegetables, legumes, and fruit intake was significantly inverse. Finally, as described previously (24), categorical variables based on the predicted dietary intake distribution in the calibration model have to be interpreted with caution, because the predicted variation does not reflect true variation.

The most important strength of our study is its sample size. To our knowledge, this is the largest observational cohort of diabetic individuals that investigated associations between lifestyle factors and mortality. Furthermore, the multicentric design with centers spread across Europe enabled the coverage of a large variation in exposures. Also, we controlled for important risk factors in our analyses, including the age at diabetes diagnosis and treatment with insulin. Additionally, the application of a competing risk model allowed the evaluation of several outcomes at the same time without losing statistical power due to exclusion of subjects.

In conclusion, our study showed that a diet high in vegetables, legumes, and fruit was associated with a reduced risk of all-cause mortality in a European diabetic population. Vegetables, legumes and fruit seemed to have impact especially on CVD mortality, and not on cancer mortality. Our study lends support to the current state of evidence from general population studies that the protective potential of high vegetable and fruit intake is larger for CVD than for cancer. Furthermore, our study underlines the recommendation for the diabetic population to eat large amounts of vegetables, legumes, and fruit.

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