Mediterranean diet adherence and risk of pancreatic cancer: A pooled analysis of two Dutch cohorts

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3w?›Studies investigating the association of Mediterranean diet (MD) adherence with pancreatic cancer risk are limited and had inconsistent results. We examined the association between MD adherence and pancreatic cancer incidence by pooling data from the Netherlands Cohort Study (NLCS, 120,852 subjects) and the Dutch cohort of the European Prospective Investigation into Cancer and Nutrition (EPIC-NL, 40,011 subjects). MD adherence was assessed using alternate and modified Mediterranean diet scores (aMED and mMED, respectively), including and excluding alcohol. After median follow-ups of 20.3 (NLCS) and 19.2 (EPIC-NL) years, 449 microscopically confirmed pancreatic cancer (MCPC) cases were included in study-specific multivariable Cox models. Study-specific estimates were pooled using a random-effects model. MD adherence was not significantly associated with MCPC risk in pooled and study-specific analyses, regardless of sex and MD score. Pooled hazard ratios (95% confidence interval) for high (6–8) compared to low (0–3) values of mMED excluding alcohol were 0.66 (0.40–1.10) in men and 0.94 (0.63–1.40) in women. In never smokers, mMED excluding alcohol seemed to be inversely associated with MCPC risk (nonsignificant). However, no association was observed in ever smokers ($p_{heterogeneity}$ = 0.03). Hazard ratios were consistent across strata of other potential effect modifiers. Considering MD scores excluding alcohol, mMED-containing models generally fitted better than aMED-containing models, particularly in men. Although associations somewhat differed when all pancreatic cancers were considered instead of MCPC, the overall conclusion was similar. In conclusion, MD adherence was not associated with pancreatic cancer risk in a pooled analysis of two Dutch cohorts.

Introduction

Despite its relatively low incidence, pancreatic cancer was ranked as the third most common cause of cancer death in the United States (US) based on 2010–2014 data.[1] Because the early disease stages are usually asymptomatic, pancreatic cancer is generally diagnosed in advanced disease stages resulting

What's new?

Adherence to the Mediterranean diet, characterized primarily by a high intake of plant-based foods, is associated with reduced risks of several cancers. In the case of pancreatic cancer, however, in which dietary factors are suspected of playing a significant role, evidence remains inconclusive. In this pooled analysis of two Dutch cohorts, no association was found between Mediterranean diet adherence and risk of microscopically confirmed pancreatic cancer (MCPC). The outcome was unaffected by sex and type of Mediterranean diet score used. MCPC risk may be inversely related to Mediterranean diet adherence in never smokers, though statistical analysis did not reach significance.

in a poor prognosis; 5-year survival rates of pancreatic cancer in the US (2007–2013) were only 8.2% for all stages and 2.7% for distant stages.[2,3] Diet could be a modifiable target for the primary prevention of pancreatic cancer. However, the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) judged in their 2012 report on pancreatic cancer that the evidence supporting an association between dietary factors and pancreatic cancer is limited.[2] Only body fatness (convincing evidence) and greater childhood growth (probable evidence) were reported to be associated with an increased pancreatic cancer risk.[2]

The plant-based traditional Mediterranean dietary pattern (MD) is characterized by a high intake of vegetables, legumes, fruits, nuts, whole grains, olive oil [rich in monounsaturated fatty acids (MUFA)] and fish. In contrast, high-fat dairy products, red and processed meats, refined grains and sweets are consumed in small amounts. Alcohol consumption is considered moderate in the MD.[4–6] High adherence to the MD has been shown to reduce cardiovascular disease incidence and mortality, as well as all-cause mortality.[7–9] Recently, researchers have taken an increasing interest in the potentially beneficial effect of MD adherence on cancer risk.[10]

Up until now, the association between *a priori* defined MD adherence and the incidence of pancreatic cancer has been investigated in three studies (1 case–control, 2 prospective cohorts), with inconsistent results.[11–13] An Italian hospital-based case–control study showed a statistically significantly decreased risk of pancreatic cancer with higher MD adherence.[12] On the other hand, the reduced pancreatic cancer risk associated with higher MD adherence was not significant in a US prospective cohort study[11] and there was no evidence of an association in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort.[13] In addition to the results concerning pancreatic cancer incidence, a significant decrease in pancreatic cancer mortality was associated with higher MD adherence in Swedish subjects.[14] It has previously been shown that associations of factors with pancreatic cancer risk depend on the microscopic confirmation status of the cases.[15,16] The most valid results are obtained by restricting analyses to microscopically confirmed pancreatic cancer (MCPC) cases, which minimizes misclassification of disease status.[15,16] Results for this subgroup of cases have only been reported in EPIC before.[13]

The aim of the present analysis was to prospectively investigate the association of MD adherence with pancreatic cancer risk, using various *a priori* defined MD scores with and without alcohol. Analyses were performed considering all pancreatic cancer cases and MCPC cases specifically. We investigated these aims by pooling results of the Netherlands Cohort Study (NLCS) and the Dutch EPIC (EPIC-NL) cohort to increase the statistical power.

Materials and Methods
Study population and pancreatic cancer follow-up
A pooled analysis was conducted including individual participant data from the NLCS and EPIC-NL cohorts. Detailed descriptions of both cohorts have been published previously.[17–23] In short, the NLCS is a nationwide population-based cohort study among 58,279 men and 62,573 women from 204 Dutch municipalities, who were aged between 55 and 69 years at enrollment.[17] At baseline in September 1986, participants completed a self-administered questionnaire on diet and other cancer risk factors. For efficiency, data were processed and analyzed using the nested case–cohort design. Therefore, cases were derived from the entire NLCS cohort, whereas the number of person-years at risk was estimated based on a subcohort ($n = 5,000$). Subcohort members were randomly sampled immediately after baseline and were followed-up biennially for vital status information using municipal population registries.[17,20,24] The EPIC-NL cohort comprises 40,011 subjects, who were included in the EPIC-Prospect (17,357 women, aged 49–70 years) or EPIC-MORGEN (10,260 men and 12,394 women, aged 20–65 years) cohorts.[21–23] Cohort members of EPIC-Prospect were participants of a breast cancer screening program in the region of Utrecht between 1993 and 1997, whereas EPIC-MORGEN was composed by selecting random population samples of three Dutch towns (Amsterdam, Maastricht and Doetinchem) in the same time period. Baseline measurements were performed using a general questionnaire and a food frequency questionnaire (FFQ). In addition, physical examinations, including measurements of height, weight and blood pressure, were carried out at baseline. Vital status information of EPIC-NL participants was retrieved *via* linkage with the municipal population registries.[21–23] The NLCS and EPIC-NL cohorts were approved by the internal review boards of the institutions involved. All study participants consented to participation by completing the questionnaire (NLCS) or signing an informed consent form (EPIC-NL).

Incident cases of pancreatic cancer (International Classification of Diseases for Oncology, Third Edition (ICD-O-3), code C25) were identified by annual record linkage with the Netherlands Cancer Registry and PALGA, the nationwide

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Dutch Pathology Registry.[18,23] Cases with endocrine pancreatic cancer, defined by ICD-O-3 code C25.4 or an endocrine tumor type, were excluded and censored at their date of diagnosis. Pancreatic cancer cases were considered to have MCPC, when they were diagnosed based on hematological, cytological or histological confirmation. Subjects were excluded from the analyses if they met one of the following criteria: prevalent cancer at baseline, except nonmelanoma skin cancer (EPIC-NL) or any type of skin cancer (NLCS), or missing; incomplete, inconsistent or missing (dietary) questionnaires; a ratio of energy intake to basal metabolic rate in the lowest or highest 0.5% (EPIC-NL only); or incomplete data on alcohol consumption and variables necessary to calculate MD adherence. In total, 4,084 of the NLCS subcohort members were eligible for inclusion in the analyses. In the EPIC-NL cohort, 35,459 subjects met the eligibility criteria. Using 20.3 years of follow-up, 651 cases of exocrine pancreatic cancer (391 MCPC) were diagnosed in the NLCS. In the EPIC-NL cohort, 142 cases (104 MCPC) were detected in a median follow-up of 19.2 years. Observations were censored at December 31, 2006 (NLCS) and December 31, 2014 (EPIC-NL). The selection process of subjects eligible for inclusion in the analyses is visualized in the flow diagrams in Supporting Information Figure S1 (NLCS) and Supporting Information Figure S2 (EPIC-NL).

Exposure assessment

The habitual dietary intake over the year preceding enrollment was assessed by study-specific, self-administered, semi-quantitative FFQs, of which the validity and reproducibility have been evaluated.[19,25–27] Dutch food composition (NEVO) tables from the years 1986 (NLCS) and 1998 (EPIC-NL) were utilized to calculate mean daily nutrient intakes.[28]

Mediterranean diet adherence

Relative MD adherence was assessed using the alternate and modified Mediterranean diet scores (aMED and mMED, respectively), which are two variants of the original traditional Mediterranean diet score (tMED) developed by Trichopoulou et al.[29–33] Before calculation of the MD scores, food intakes were adjusted to total energy intakes of 2,000 (women) and 2,500 (men) kilocalories (kcal) per day to correct for differences in daily energy intakes.[29,33] aMED is calculated based on the daily intakes of nine dietary components, which are each scored by 0 or 1 points, resulting in a sum score ranging from 0 (minimal MD adherence) to 9 (maximal MD adherence).[32,33] A score of 1 is assigned to: high intakes (≥ sex-specific median) of vegetables (excluding potatoes), legumes, fruits, nuts, whole grains, and fish; a high (≥ sex-specific median) ratio of MUFA to saturated fatty acids (SFA); a low intake (< sex-specific median) of red and processed meats; and a moderate alcohol intake (5–25 grams per day (g/day) for both sexes).[32,33] aMED is calculated in a similar way as tMED, but differs from the original score with respect to the composition of the dietary components. In tMED[29,30] fruits

and nuts are combined, total intakes of cereals and meats are considered, and consumption of dairy products is included (1 point if < sex-specific median). Besides, moderate alcohol consumption is defined differently in men (10–50 g/day) and women (5–25 g/day).[29,30] mMED[31] was specifically developed for usage in non-Mediterranean populations and differs from tMED with respect to the fatty acid ratio included. In mMED, the ratio of unsaturated fatty acids (polyunsaturated fatty acids (PUFA) + MUFA) to SFA replaces the MUFA:SFA ratio.[31] Sex-specific median intakes of dietary components were calculated separately for the NLCS and EPIC-NL cohorts. We also created reduced variants of aMED and mMED without alcohol (aMEDr and mMEDr, respectively), because moderate/heavy alcohol consumption (>3 drinks per day) might increase pancreatic cancer risk.[2,34] aMEDr and mMEDr ranged from 0 to 8 points. Based on their MD score, subjects were categorized as having low (0–3), middle (4–5) or high (6–8(9)) levels of MD adherence.[31,33] Additionally, MD scores were included as continuous terms to obtain effect estimates per two-point increment in score.

Statistical analyses

All analyses were performed separately for men and women unless otherwise specified. As a general approach, we first determined study-specific (NLCS and EPIC-NL) estimates, which were pooled in a later stage.

Cox proportional hazards models with follow-up as time variable were run to estimate study-specific hazard ratios (HRs) and 95% confidence intervals (95% CIs) for the relation between MD adherence and pancreatic cancer incidence. (Sub)cohort members were considered to be at risk from baseline until pancreatic cancer diagnosis, death, emigration, loss to follow-up or end of follow-up, whichever came first. Since the case–cohort design introduces additional variance, the Huber-White sandwich estimator was used to estimate standard errors of the HRs in the NLCS cohort.[35] Scaled Schoenfeld residuals tests and –ln(–ln) survival plots were used to evaluate the proportional hazards (PH) assumption.[36] In case of potential violations of the PH assumption for covariates, it was checked whether inclusion of a time-varying covariate altered the effect estimates of the exposures of interest.

aMEDr and mMEDr were modeled as both categorical and continuous variables. In order to perform tests for trends across the MD adherence categories, study- and sex-specific median values among (sub)cohort members were assigned to the MD adherence categories. Next, the created variable was fitted as a continuous term in the Cox model and statistical significance of the regression coefficient was assessed by the Wald test. Based on the literature, the following potential confounders were included in multivariable Cox models: age at baseline, sex (except for sex-specific analyses), cigarette smoking status, cigarette smoking frequency, cigarette smoking duration, body mass index (BMI), total daily energy intake, alcohol consumption (except for models containing the

original MD scores including alcohol), history of (type 2) diabetes, level of education, and (nonoccupational) physical activity. Cigarette smoking frequency and duration were combined into pack-years of smoking in the EPIC-NL cohort. Models based on NLCS data were additionally adjusted for family history of pancreatic cancer (not available for EPIC-NL), whereas the EPIC-NL models were also adjusted for cohort (EPIC-Prospect or EPIC-MORGEN).

Study-specific HRs were combined using a DerSimonian and Laird random-effects model to obtain pooled effect estimates for the association between MD adherence and pancreatic cancer risk. Weights were assigned to the study-specific estimates based on the inverse of their variances.[37,38]

The fits of aMEDr- and mMEDr-containing models (study-specific) were compared using Akaike's Information Criterion (AIC).[39] In addition, AIC was used to compare performances of study-specific models containing MD score variants with and without alcohol. To evaluate whether the relation between MD adherence and pancreatic cancer risk is influenced by the microscopic confirmation status of the cases, we also restricted the analyses to MCPC cases. This article will mainly focus on results obtained among MCPC cases, as the most valid results are obtained in this case group.[15,16] Because moderate/heavy alcohol consumption might increase the risk of pancreatic cancer, we give priority to the use of MD scores without alcohol.[2,34]

Furthermore, it was evaluated whether the relation between MD adherence and pancreatic cancer risk varied across strata of potential effect modifiers. HRs for strata of cigarette smoking status, BMI, alcohol consumption and history of diabetes were retrieved by pooling study-specific effect estimates. Similarly, pooled regression coefficients were obtained for interaction terms between the MD scores and the potential effect modifiers and significance of the interactions was tested. Finally, because preclinical disease could potentially alter a subject's diet and therefore influence the observed association between MD adherence and pancreatic cancer risk, sensitivity analyses excluding the first 2 years of follow-up were performed on the individual study level. Statistical analyses were performed using Stata15 (StataCorp LLC, College Station, TX). All presented *p*-values are two-sided. Statistical significance was defined as a *p*-value below 0.05.

Results

After median follow-up times of 20.3 (NLCS) and 19.2 (EPIC-NL) years, 793 (men: 378; women: 415) eligible cases of exocrine pancreatic cancer were diagnosed in the total study population of whom 495 (men: 245; women: 250) were microscopically confirmed.

Study-specific baseline characteristics of the included cohorts are presented in Tables 1 and 2. As expected, mean

Table 1. Baseline characteristics of the NLCS subcohort, all pancreatic cancer cases and microscopically confirmed pancreatic cancer cases

	Men						Women					
	NLCS subcohort		Pancreatic cancer cases				NLCS subcohort		Pancreatic cancer cases			
			All		MCPC				All		MCPC	
	n = 2,057		*n* = 345		*n* = 214		*n* = 2,027		*n* = 306		*n* = 177	
aMEDr	3.9	(1.6)	3.8	(1.6)	3.9	(1.6)	4.0	(1.6)	3.9	(1.6)	4.0	(1.5)
mMEDr	4.0	(1.5)	4.0	(1.4)	3.9	(1.3)	4.0	(1.5)	3.9	(1.5)	4.0	(1.5)
Age (years)[1]	61	(7)	61	(6)	61	(6)	61	(7)	63	(7)	62	(8)
Current cigarette smokers (%)	35.1		44.9		43.9		21.3		27.1		29.9	
Cigarette smoking frequency (cig/day)[1,2]	15	(10)	15	(10)	15	(10)	10	(13)	10	(10)	10	(10)
Cigarette smoking duration (years)[1,2]	36	(17)	40	(14)	40	(16)	30	(20)	30	(20)	33	(18)
Higher vocational education or university (%)	19.3		21.9		22.5		9.5		9.2		10.8	
Alcohol consumption (g/day)[1]	9.7	(20.9)	11.1	(26.4)	10.5	(26.9)	1.6	(7.8)	2.5	(9.4)	3.2	(9.6)
Daily energy intake (kcal)[1]	2,126	(648)	2,127	(653)	2,156	(585)	1,655	(516)	1,687	(499)	1,672	(511)
Body mass index (kg/m²)[1]	24.8	(3.1)	25.1	(3.5)	25.2	(3.1)	24.5	(4.2)	25.0	(3.9)	25.2	(4.3)
Nonoccupational physical activity ›60 min/day (%)	50.7		48.3		53.1		44.3		46.7		44.6	
Family history of pancreatic cancer (%)	1.0		2.0		0.9		1.0		3.6		2.8	
History of diabetes (%)	3.3		7.3		7.0		3.4		3.9		5.1	

The % missing values was ‹5% for all variables included in this table, with the exception of cigarette smoking frequency (5.9%) in men. Mean (SD) values are reported unless otherwise specified.
Abbreviations: NLCS, Netherlands Cohort Study; MCPC, microscopically confirmed pancreatic cancer; n, number of subjects; aMEDr, alternate Mediterranean diet score without the alcohol component; mMEDr, modified Mediterranean diet score without the alcohol component; cig/day, cigarettes per day; g/day, grams per day; kcal, kilocalories; kg/m², kilograms per meter²; min/day, minutes per day; SD, standard deviation; IQR, interquartile range.
[1]Median values (IQR) are reported.
[2]Median values (IQR) for frequency and duration of smoking were based on former and current smokers.

Table 2. Baseline characteristics of the total EPIC-NL cohort, all pancreatic cancer cases and microscopically confirmed pancreatic cancer cases

	Men						Women					
	EPIC-NL cohort		Pancreatic cancer cases				EPIC-NL cohort		Pancreatic cancer cases			
			All		MCPC				All		MCPC	
	n = 9,211		n = 33		n = 31		n = 26,248		n = 109		n = 73	
aMEDr	4.0	(1.6)	3.6	(1.5)	3.6	(1.5)	4.0	(1.6)	4.3	(1.6)	4.2	(1.5)
mMEDr	4.0	(1.6)	3.9	(1.1)	4.0	(1.1)	4.0	(1.6)	4.2	(1.5)	4.1	(1.4)
EPIC-MORGEN (%)	100		100		100		40.6		17.4		16.4	
Age (years)[1]	44	(18)	52	(10)	52	(11)	53	(12)	60	(9)	57	(10)
Current cigarette smokers (%)	35.8		54.6		54.8		27.5		22.9		24.7	
Pack-years of cigarette smoking (pack-years)[1,2]	14.4	(20.0)	21.8	(24.0)	21.0	(20.0)	11.3	(17.9)	17.8	(21.2)	19.4	(23.1)
Higher vocational education or university (%)	27.5		24.2		25.8		18.1		15.6		13.7	
Alcohol consumption (g/day)[1]	11.7	(22.0)	16.1	(34.2)	13.3	(35.1)	3.4	(11.4)	3.6	(14.0)	3.7	(14.9)
Daily energy intake (kcal)[1]	2,509	(857)	2,475	(762)	2,475	(776)	1,823	(584)	1,722	(505)	1,725	(505)
Body mass index (kg/m²)[1]	25.5	(4.4)	26.2	(4.6)	26.2	(4.7)	25.0	(5.1)	25.7	(4.2)	25.5	(4.2)
(Moderately) physically active (%)[3]	70.2		66.7		64.5		67.1		59.6		56.2	
History of type 2 diabetes (%)	1.1		0.0		0.0		1.7		6.4		5.5	

The % missing values in the total EPIC-NL cohort was <5% for all variables included in this table. Mean (SD) values are reported unless otherwise specified.
Abbreviations: EPIC-NL, the Dutch cohort of the European Prospective Investigation into Cancer and Nutrition; MCPC, microscopically confirmed pancreatic cancer; n, number of subjects; aMEDr, alternate Mediterranean diet score without the alcohol component; mMEDr, modified Mediterranean diet score without the alcohol component; EPIC, European Prospective Investigation into Cancer and Nutrition; g/day, grams per day; kcal, kilocalories; kg/m², kilograms per meter²; SD, standard deviation; IQR, interquartile range.
[1]Median values (IQR) are reported.
[2]Median value (IQR) in former and current smokers.
[3]Physical activity was assessed using the Cambridge Physical Activity Index, which incorporates both recreational and occupational physical activity.

MD score values in the cohorts were similar. In contrast, noteworthy age differences were observed between the cohorts, with a substantially higher median age in the NLCS. Within the EPIC-NL cohort, women were older than men. Compared to EPIC-NL participants, NLCS participants were less often current smokers (women only), lower educated, less physically active, had lower daily intakes of energy and alcohol, had a lower BMI and were more likely to have a history of diabetes. The described differences between the cohorts might (partly) be attributed to variations in age and other study characteristics, such as participant recruitment criteria, time period of study, measurement methods and variable definitions.

As is shown in Tables 1 and 2, mean MD score values were similar for MCPC cases and (sub)cohort members, except for aMEDr in EPIC-NL. Compared to (sub)cohort members, MCPC cases were older (EPIC-NL only), consumed more alcohol, had a higher BMI and were more likely to have a history of diabetes. MCPC cases were also more often current smokers. However, this did not apply for female MCPC cases in EPIC-NL, who were less often current smokers.

Tables 3 and 4 present pooled and study-specific results of the multivariable Cox proportional hazards analyses evaluating sex-specific associations of MD adherence, measured by various MD scores, with MCPC risk. Due to missing values in

covariates, 46 (9.3%) MCPC cases [NLCS: 43 (11.0%); EPIC-NL: 3 (2.9%)] and 1,307 (3.3%) (sub)cohort members [NLCS: 364 (8.9%); EPIC-NL: 943 (2.7%)] could not be included in the multivariable Cox proportional hazards analyses.

MD adherence was not statistically significantly associated with MCPC risk among men in the pooled multivariable analyses (Table 3). Pooled HRs (95% CI) comparing high to low MD adherence were 0.70 (0.44–1.12) and 0.66 (0.40–1.10) for aMEDr and mMEDr, respectively. Although the HR was not significant, middle mMEDr values seemed to be associated with an increased risk of MCPC. There was also no evidence of an association between MD adherence and MCPC risk when HRs were estimated per two-point increment in MD score (aMEDr = 0.96, 95% CI: 0.80–1.16; mMEDr = 0.99, 95% CI: 0.83–1.18). The observed associations were consistent among the individual cohorts (Table 3). The −ln(−ln) survival plots indicated a potential violation of the PH assumption for the MD scores in men in the EPIC-NL cohort. However, PH assumption tests were not statistically significant. Furthermore, results generally similar to those for MCPC were obtained when all pancreatic cancer cases were included in the analyses (Supporting Information Table S1).

As in men, we observed no association between MD adherence and MCPC risk among women in the pooled

Table 3. Associations of aMED and mMED (in- and excluding alcohol) with microscopically confirmed pancreatic cancer risk in men

Cohort	Alcohol	Measure	aMED 0–3	aMED 4–5	aMED 6–8[1]	aMED p_trend	aMED Continuous[2]	mMED 0–3	mMED 4–5	mMED 6–8[1]	mMED p_trend	mMED Continuous[2]
NLCS	Excluding alcohol	N cases/PY_subcohort	83/11,934	80/12,620	24/4,809		187/29,363	65/10,970	102/13,580	20/4,814		187/29,363
		HR_age (95% CI)[3]	1.00	0.91 (0.66–1.26)	0.70 (0.44–1.13)	0.144	0.95 (0.79–1.15)	1.00	1.25 (0.90–1.73)	0.69 (0.41–1.16)	0.188	0.96 (0.80–1.15)
		HR_fully adjusted (95% CI)[4]	1.00	0.93 (0.66–1.30)	0.73 (0.44–1.21)	0.225	0.98 (0.80–1.20)	1.00	1.31 (0.93–1.84)	0.69 (0.41–1.18)	0.210	0.97 (0.80–1.17)
	Including alcohol	N cases/PY_subcohort	65/9,277	84/13,072	38/7,014		187/29,363	40/7,821	111/14,133	36/7,409		187/29,363
		HR_fully adjusted (95% CI)[5]	1.00	0.95 (0.67–1.34)	0.80 (0.51–1.26)	0.392	0.92 (0.76–1.10)	1.00	1.50 (1.01–2.24)	0.91 (0.56–1.48)	0.301	0.95 (0.80–1.13)
EPIC-NL	Excluding alcohol	N cases/PY_cohort	14/64,824	13/70,567	3/31,053		30/166,444	11/64,065	17/73,238	2/29,141		30/166,444
		HR_age (95% CI)[6]	1.00	0.84 (0.39–1.79)	0.42 (0.12–1.45)	0.164	0.78 (0.50–1.21)	1.00	1.22 (0.57–2.60)	0.34 (0.08–1.55)	0.189	0.97 (0.61–1.53)
		HR_fully adjusted (95% CI)[7]	1.00	0.94 (0.44–2.02)	0.52 (0.14–1.86)	0.323	0.87 (0.55–1.38)	1.00	1.39 (0.64–3.01)	0.46 (0.10–2.12)	0.412	1.15 (0.71–1.87)
	Including alcohol	N cases/PY_cohort	12/50,128	14/70,079	4/46,237		30/166,444	8/47,054	16/74,225	6/45,166		30/166,444
		HR_fully adjusted (95% CI)[8]	1.00	0.92 (0.42–2.02)	0.44 (0.14–1.42)	0.165	0.92 (0.60–1.42)	1.00	1.32 (0.56–3.13)	0.86 (0.29–2.56)	0.993	1.07 (0.68–1.69)
Pooled[9]	Excluding alcohol	N cases	97	93	27		217	76	119	22		217
		HR_fully adjusted (95% CI)	1.00	0.93 (0.68–1.26)	0.70 (0.44–1.12)	0.135	0.96 (0.80–1.16)	1.00	1.32 (0.97–1.81)	0.66 (0.40–1.10)	0.144	0.99 (0.83–1.18)
	Including alcohol	N cases	77	98	42		217	48	127	42		217
		HR_fully adjusted (95% CI)	1.00	0.94 (0.68–1.30)	0.74 (0.49–1.13)	0.208	0.92 (0.77–1.09)	1.00	1.47 (1.02–2.11)	0.90 (0.58–1.41)	0.342	0.97 (0.82–1.14)

Abbreviations: aMED, alternate Mediterranean diet score; mMED, modified Mediterranean diet score; NLCS, Netherlands Cohort Study; n, number of subjects; PY, person-years in the (sub)cohort; HR, hazard ratio; CI, confidence interval; EPIC-NL, the Dutch cohort of the European Prospective Investigation into Cancer and Nutrition; EPIC, European Prospective Investigation into Cancer and Nutrition; CPAI, Cambridge Physical Activity Index.

[1]The highest score category of the aMED/mMED including alcohol was defined as 6–9 points.
[2]Continuous HRs were estimated per two-point increment in score.
[3]The age-adjusted model was adjusted for age at baseline (years).
[4]The fully adjusted model was in addition to 3 adjusted for cigarette smoking status (never, former, current), cigarette smoking frequency (cigarettes smoked per day, centered), cigarette smoking duration (years, centered), body mass index (kilograms per meter²), daily energy intake (kilocalories), alcohol consumption (grams per day), history of diabetes (no, yes), family history of pancreatic cancer (no, yes), highest level of education (primary school or lower vocational, secondary school or medium vocational, higher vocational or university), and nonoccupational physical activity (≤30, >30-≤60, >60-≤90, >90 minutes per day).
[5]This model was adjusted for the same variables as 4 with the exception of alcohol consumption.
[6]The age-adjusted model was adjusted for age at baseline (years) and cohort (EPIC-Prospect, EPIC-MORGEN).
[7]The fully adjusted model was in addition to 6 adjusted for cigarette smoking status (never, former, current), pack-years of cigarette smoking (pack-years, centered), body mass index (kilograms per meter²), daily energy intake (kilocalories), alcohol consumption (grams per day), history of type 2 diabetes (no, yes), highest level of education (primary school or lower vocational, secondary school or medium vocational, higher vocational or university), and total physical activity (CPAI, missings imputed: inactive, moderately inactive, moderately active, active).
[8]This model was adjusted for the same variables as 7 with the exception of alcohol consumption.
[9]Study-specific effect estimates were pooled using the DerSimonian and Laird random-effects model.

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Table 4. Associations of aMED and mMED (including and excluding alcohol) with microscopically confirmed pancreatic cancer risk in women

			aMED					mMED				
			0-3	4-5	6-8[1]	p_trend	Continuous[2]	0-3	4-5	6-8[1]	p_trend	Continuous[2]
NLCS	Excluding alcohol	N cases/PY_subcohort	57/12,267	76/15,124	28/6,277		161/33,668	69/11,670	66/16,525	26/5,474		161/33,668
		HR_age (95% CI)[3]	1.00	1.09 (0.76–1.55)	0.97 (0.61–1.55)	0.903	0.99 (0.81–1.22)	1.00	0.68 (0.48–0.96)	0.81 (0.51–1.30)	0.357	0.96 (0.78–1.20)
		HR_fully adjusted (95% CI)[4]	1.00	1.12 (0.78–1.63)	1.07 (0.66–1.75)	0.765	1.03 (0.83–1.27)	1.00	0.71 (0.49–1.01)	0.85 (0.53–1.38)	0.484	0.99 (0.79–1.24)
	Including alcohol	N cases/PY_subcohort	49/10,747	74/14,699	38/8,223		161/33,668	53/9,692	75/16,589	33/7,387		161/33,668
		HR_fully adjusted (95% CI)[5]	1.00	1.14 (0.78–1.67)	1.07 (0.67–1.70)	0.836	1.04 (0.84–1.27)	1.00	0.85 (0.58–1.23)	0.82 (0.51–1.31)	0.441	1.00 (0.80–1.24)
EPIC-NL	Excluding alcohol	N cases/PY_cohort	23/185,706	31/199,304	17/86,273		71/471,283	22/179,756	36/211,521	13/80,006		71/471,283
		HR_age (95% CI)[6]	1.00	1.13 (0.66–1.95)	1.44 (0.77–2.70)	0.253	1.16 (0.86–1.55)	1.00	1.26 (0.74–2.15)	1.21 (0.61–2.40)	0.600	1.08 (0.80–1.47)
		HR_fully adjusted (95% CI)[7]	1.00	1.11 (0.64–1.93)	1.41 (0.73–2.70)	0.299	1.14 (0.84–1.55)	1.00	1.23 (0.72–2.11)	1.15 (0.57–2.34)	0.724	1.05 (0.76–1.45)
	Including alcohol	N cases/PY_cohort	18/155,656	34/196,121	19/119,506		71/471,283	17/147,114	37/210,838	17/113,331		71/471,283
		HR_fully adjusted (95% CI)[8]	1.00	1.35 (0.76–2.41)	1.23 (0.63–2.41)	0.670	1.13 (0.85–1.51)	1.00	1.35 (0.75–2.42)	1.15 (0.57–2.30)	0.870	1.13 (0.77–1.42)
Pooled[9]	Excluding alcohol	N cases	80	107	45		232	91	102	39		232
		HR_fully adjusted (95% CI)	1.00	1.12 (0.83–1.52)	1.18 (0.80–1.75)	0.395	1.07 (0.89–1.27)	1.00	0.90 (0.52–1.54)	0.94 (0.63–1.40)	0.748	1.01 (0.84–1.21)
	Including alcohol	N cases	67	108	57		232	70	112	50		232
		HR_fully adjusted (95% CI)	1.00	1.20 (0.87–1.65)	1.12 (0.76–1.64)	0.677	1.07 (0.90–1.26)	1.00	1.01 (0.65–1.57)	0.91 (0.62–1.34)	0.600	1.01 (0.85–1.21)

Abbreviations: aMED, alternate Mediterranean diet score; mMED, modified Mediterranean diet score; NLCS, Netherlands Cohort Study; n, number of subjects; PY, person-years in the (sub)cohort; HR, hazard ratio; CI, confidence interval; EPIC-NL, the Dutch cohort of the European Prospective Investigation into Cancer and Nutrition; EPIC, European Prospective Investigation into Cancer and Nutrition; CPAI, Cambridge Physical Activity Index.

1 The highest score category of the aMED/mMED including alcohol was defined as 6–9 points.
2 Continuous HRs were estimated per two-point increment in score.
3 The age-adjusted model was adjusted for age at baseline (years).
4 The fully adjusted model was in addition to 3 adjusted for cigarette smoking status (never, former, current), cigarette smoking frequency (cigarettes smoked per day, centered), cigarette smoking duration (years, centered), body mass index (kilograms per meter²), daily energy intake (kilocalories), alcohol consumption (grams per day), history of diabetes (no, yes), family history of pancreatic cancer (no, yes), highest level of education (primary school or lower vocational, secondary school or medium vocational, higher vocational or university), and nonoccupational physical activity (≤30, >30- ≤60, >60- ≤90, >90 minutes per day).
5 This model was adjusted for the same variables as 4 with the exception of alcohol consumption.
6 The age-adjusted model was adjusted for age at baseline (years) and cohort (EPIC-Prospect, EPIC-MORGEN).
7 The fully adjusted model was in addition to 6 adjusted for cigarette smoking status (never, former, current), pack-years of cigarette smoking (pack-years, centered), body mass index (kilograms per meter²), daily energy intake (kilocalories), alcohol consumption (grams per day), history of type 2 diabetes (no, yes), highest level of education (primary school or lower vocational, secondary school or medium vocational, higher vocational or university), and total physical activity (CPAI, missings imputed: inactive, moderately inactive, moderately active, active).
8 This model was adjusted for the same variables as 7 with the exception of alcohol consumption.
9 Study-specific effect estimates were pooled using the DerSimonian and Laird random-effects model.

multivariable analyses (Table 4). Pooled HRs (95% CI) per two-point increment in score were 1.07 (0.89–1.27) and 1.01 (0.84–1.21) for aMEDr and mMEDr, respectively. Associations seemed to differ between the individual cohorts, particularly when MD adherence was expressed using mMEDr categories. Overall, mMEDr was not associated with MCPC risk in the NLCS, though a nonsignificantly reduced MCPC risk seemed to be associated with middle mMEDr values (HR$_{middle\ vs.\ low}$ = 0.71, 95% CI: 0.49–1.01). In contrast to the NLCS findings, associations between the categorical mMEDr and MCPC risk were absent or slightly positive in EPIC-NL. There was also no evidence of an association between MD adherence and pancreatic cancer risk in women when all pancreatic cancer cases were included in the analyses (Supporting Information Table S2).

Study-specific tests for heterogeneity between the sexes were mostly not statistically significant, except when MD adherence was assessed by mMEDr categories in the NLCS. Comparing study-specific AIC values, we found that mMEDr-containing models generally fitted better than models containing aMEDr, particularly in men. In women, this pattern was unclear. Also, no consistent pattern was observed when performances of models containing MD scores with and without alcohol were compared.

Table 5 shows pooled associations between MD adherence and the risk of MCPC within strata of potential effect modifiers. Since study-specific tests for heterogeneity between the sexes were not statistically significant when MD adherence was modeled using continuous MD scores, study-specific subgroup results based on both sexes were pooled to increase the statistical power. The association between mMEDr and MCPC risk differed statistically significantly across the strata of cigarette smoking status ($p_{heterogeneity}$ = 0.03). Although not significant, mMEDr seemed to be inversely associated with MCPC risk in never smokers, whereas there was no evidence of an inverse association in ever smokers. A similar, but weaker and nonsignificant, pattern was noticed when MD adherence was assessed using aMEDr. No differences in associations were observed across strata of BMI, alcohol consumption and history of diabetes. Finally, exclusion of the first 2 years of follow-up did not alter the study-specific results. However, in the NLCS, we did note a nonsignificant inverse association between MD adherence and MCPC risk when focusing on the first 2 years of follow-up. In EPIC-NL, too few cases were available to perform this analysis.

Discussion

MD adherence was not significantly associated with MCPC risk in pooled multivariable analyses, including NLCS and EPIC-NL data, as well as study-specific multivariable analyses, regardless of sex and MD score used. The model fit was generally better for mMEDr-containing models compared to aMEDr-containing models, especially in men. Comparison of performances of models containing MD scores with and

without alcohol did not show a consistent pattern. Stratified analyses indicated an inverse association between mMEDr and MCPC risk in never smokers (nonsignificant), but not in ever smokers ($p_{heterogeneity}$ = 0.03). There was no evidence for effect modification by BMI, alcohol consumption or history of diabetes.

Results of our pooled analysis are in line with those obtained in previous prospective cohort studies[11,13] that did also not find a statistically significant inverse association between MD adherence and pancreatic cancer incidence. In diabetes-free participants of the National Institutes of Health-American Association of Retired Persons (NIH-AARP) Diet and Health Study, a HR of 0.92 (95% CI: 0.81–1.05) was observed when comparing high (aMEDr: 5–8) to low (0–4) MD adherence.[11] In the same study, a nonsignificantly reduced pancreatic cancer risk was found when scores of 7–8 were compared to scores of 0–1 (p = 0.06). Furthermore, there was no indication for an inverse association between MD adherence, assessed by a variant of the relative Mediterranean diet score excluding alcohol, and pancreatic cancer risk in the EPIC cohort (HR$_{high\ vs.\ low}$ = 0.99, 95% CI: 0.77–1.26).[13] In contrast, an Italian hospital-based case–control study did show a statistically significant inverse association between MD adherence (revised tMED including alcohol) and pancreatic cancer incidence (odds ratio$_{≥6\ vs.\ <3}$ = 0.48, 95% CI: 0.35–0.67).[12] Additionally, higher MD adherence according to an adapted version of mMED including alcohol was associated with a significant decrease in pancreatic cancer mortality in the prospective Västerbotten Intervention Program with a HR of 0.82 (95% CI: 0.72–0.94) per one-point increment in score.[14] However, the results of the latter study were based on only 92 pancreatic cancer deaths and might have been distorted by selection bias as excluded participants were characterized by a higher mortality risk.

The main results of the present study were based on analyses that were restricted to MCPC cases. Restricting the analyses to MCPC cases minimizes misclassification of disease status and therefore renders the most valid results.[15,16] Non-MCPC cases may present with different subtypes of pancreatic cancer or nonpancreatic cancer. This could affect the observed association when these subtypes or nonpancreatic cancers are differentially related to the exposure of interest compared to MCPC.[16] Although we observed some differences between associations determined among all pancreatic cancer cases and MCPC cases in the present analysis, the overall conclusion was similar for both case sets. Of the previously conducted studies concerning MD adherence and pancreatic cancer risk, only the EPIC study by Molina-Montes *et al.*[13] reported results in MCPC cases specifically and concluded that exclusion of non-MCPC cases did not alter the effect estimates.

Dietary habits may be influenced by the presence of preclinical disease, in particular in case of gastrointestinal

Table 5. Pooled results for fully adjusted associations[1] of aMEDr and mMEDr with microscopically confirmed pancreatic cancer risk for various subgroups

Subgroup	N cases	aMEDr (per two-point increment)			mMEDr (per two-point increment)		
		HR_{pooled}[2]	(95% CI)	$p_{heterogeneity}$[3]	HR_{pooled}[2]	(95% CI)	$p_{heterogeneity}$[3]
Overall	449	1.03	(0.90–1.16)		1.01	(0.89–1.15)	
Cigarette smoking status[4]							
Never smokers	137	0.89	(0.71–1.13)		0.81	(0.65–1.02)	
Ever smokers	312	1.08	(0.93–1.25)	0.230	1.11	(0.94–1.31)	0.034
Body mass index[5]							
≥18.5 - ‹25.0 kg/m²	203	1.03	(0.85–1.25)		1.01	(0.84–1.21)	
≥25.0 kg/m²	245	1.04	(0.87–1.24)	0.742	1.03	(0.86–1.24)	0.926
Alcohol consumption[6,7]							
›0 - ‹15.0 g/day	244	1.09	(0.92–1.28)		1.07	(0.90–1.26)	
≥15.0 g/day	139	0.89	(0.69–1.14)	0.215	0.91	(0.72–1.15)	0.264
History of diabetes[8]							
No	423	1.02	(0.89–1.16)		1.02	(0.89–1.16)	
Yes	26	1.48	(0.62–3.49)	0.634	0.80	(0.37–1.74)	0.672

Abbreviations: aMEDr, alternate Mediterranean diet score without the alcohol component; mMEDr, modified Mediterranean diet score without the alcohol component; n, number of subjects; HR, hazard ratio; CI, confidence interval; kg/m², kilograms per meter²; g/day, grams per day; NLCS, Netherlands Cohort Study; EPIC-NL, the Dutch cohort of the European Prospective Investigation into Cancer and Nutrition; EPIC, European Prospective Investigation into Cancer and Nutrition; CPAI, Cambridge Physical Activity Index.
[1]The fully adjusted analyses in the NLCS cohort were adjusted for age at baseline (years), sex (men, women), cigarette smoking status (never, former, current), cigarette smoking frequency (cigarettes smoked per day, centered), cigarette smoking duration (years, centered), body mass index (kg/m²), daily energy intake (kilocalories), alcohol consumption (g/day), history of diabetes (no, yes), family history of pancreatic cancer (no, yes), highest level of education (primary school or lower vocational, secondary school or medium vocational, higher vocational or university), and nonoccupational physical activity (≤30, ›30- ≤60, ›60- ≤ 90, ›90 minutes per day).The fully adjusted analyses in the EPIC-NL cohort were adjusted for age at baseline (years), sex (men, women), cohort (EPIC-Prospect, EPIC-MORGEN), cigarette smoking status (never, former, current), pack-years of cigarette smoking (pack-years, centered), body mass index (kg/m²), daily energy intake (kilocalories), alcohol consumption (g/day), history of type 2 diabetes (no, yes), highest level of education (primary school or lower vocational, secondary school or medium vocational, higher vocational or university), and total physical activity (CPAI, missings imputed: inactive, moderately inactive, moderately active, active).
[2]Study-specific effect estimates were pooled using the DerSimonian and Laird random-effects model.
[3]P-values for heterogeneity between subgroups were obtained by testing the statistical significance of pooled interaction terms between aMEDr/mMEDr and the potential effect modifiers.
[4]Not adjusted for cigarette smoking status.
[5]Not adjusted for body mass index.
[6]No pooled HRs could be obtained for nonconsumers of alcohol, because no microscopically confirmed cases of pancreatic cancer were diagnosed in this subgroup in the EPIC-NL cohort.
[7]Not adjusted for alcohol consumption.
[8]Not adjusted for history of (type 2) diabetes.

cancers. Preclinical disease symptoms may result in reduced intakes of Mediterranean foods, such as vegetables, fruits and nuts, by cases. This could cause case–control studies to find a protective effect, whereas in fact there is no association. With regard to MD adherence and pancreatic cancer incidence, only the case–control study by Bosetti *et al.*[12] observed a statistically significant inverse association. Moreover, in the NLCS cohort, we noted that higher MD adherence was associated with a nonsignificantly reduced MCPC risk when we only included the first 2 years of follow-up, whereas there was no evidence for a relation in later follow-up periods. This indicates that indeed the presence of preclinical disease could cause us to find an inverse association in the absence of a true effect.

Study-specific tests for heterogeneity showed that the association of MD adherence with MCPC risk did not significantly differ between the sexes in the NLCS and EPIC-NL, except when MD adherence was assessed by mMEDr categories in the NLCS. Likewise, previously conducted studies on the topic did also not observe clear differences in associations between men and women.[11–14] In our pooled analysis, the association of mMEDr, but not aMEDr, with MCPC risk differed statistically significantly across the strata of smoking status. Higher mMEDr values seemed to be associated with a decreased MCPC risk in never smokers (nonsignificant), but not in ever smokers. In contrast, previous studies did not observe an interaction with smoking status.[12–14] Future studies should further investigate the potential effect modifying role of smoking status in the association between MD adherence and pancreatic cancer risk. HRs were consistent across strata of the other potential effect modifiers that we evaluated, including history of diabetes. Similarly, there was no evidence for an interaction with diabetes status in the study by Molina-Montes *et al.*[13] In contrast, the significant inverse association between MD adherence and pancreatic cancer risk observed

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in the study by Bosetti *et al.*[12] was restricted to nondiabetics ($p_{heterogeneity}$ = 0.01).

Comparing various MD score variants, we observed that mMEDr-containing models performed better than aMEDr-containing models in men, whereas no clear pattern was present in women. In contrast, previous NLCS analyses concerning breast and lung cancer consistently showed a better performance for aMEDr-containing models.[40,41] Because moderate/heavy alcohol consumption might be associated with an increased pancreatic cancer risk,[2,34] we also compared model performances of MD score variants including and excluding alcohol component, which showed no consistent pattern. Previously conducted studies evaluating the effect of considering alcohol as MD score component, found similar HRs for MD score variants with and without alcohol.[12,13]

A major strength of our study is the pooling of data of two cohorts, which increased the statistical power. However, it should be noted that the relatively low number of male MCPC cases in the EPIC-NL cohort caused the pooled results for men to primarily reflect the associations observed in the NLCS cohort. Another strength with respect to the pooled analyses was the availability of individual participant data, which enabled us to standardize the statistical methods as well as the exposure, confounding and outcome variables, thereby minimizing between-study heterogeneity. Additionally, we had access to detailed dietary data retrieved *via* FFQs of which the validity and reproducibility have been evaluated.[19,25–27] Finally, the prospective designs and long durations of follow-up were other strengths of the included cohorts.

A potential weakness of the MD scores used, particularly in non-Mediterranean countries such as the Netherlands, is the population-dependent assignment of scores. Therefore, even though diets of subjects with higher MD scores in our study population can be considered to be more Mediterranean compared to those of subjects with lower MD scores, high MD scores do not necessarily reflect close adherence to a true MD. However, MD adherence was also not significantly associated with a reduced pancreatic cancer risk in the southern European countries of the EPIC cohort.[13] Olive oil is the principal source of fat in the traditional MD.[4,5] However, tMED[29,30] and many of its derivatives, including the MD scores that we used, do not incorporate olive oil consumption as a specific component. Instead, a fatty acid ratio is used to model the high levels of MUFA (mainly from olive oil) and low levels of SFA characteristic of the Greek MD.[29] The use of a fatty acid ratio to reflect the high olive oil intake in the traditional MD improves the usage of tMED and its derivatives in non-Mediterranean countries in which the olive oil consumption is generally low, as was also the case in the Netherlands at the time of our baseline measurements. Another weakness of our analysis was the reliance on single baseline measurements for dietary habits and potential confounding factors. Hence, changes in diet and/or confounding factors during follow-up might have attenuated the associations. However, it has been shown that the reproducibility of the FFQs used was generally good.[25–27] The NLCS-FFQ had an average test–retest correlation of 0.66 for all nutrients. After 5 years, the correlation between the baseline and repeated measurement of the NLCS-FFQ had declined on average only 0.07.[25] The FFQ used in the EPIC-NL cohort had a median 12-month reproducibility for food groups of 0.71 for men and 0.77 for women.[26] Finally, errors in the measurements of dietary habits and residual confounding by unmeasured factors cannot fully be excluded.

In conclusion, higher MD adherence was not associated with a decreased risk of pancreatic cancer in a pooled analysis of two Dutch cohorts.

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