Original Research Article

Mediterranean Diet and risk of Pancreatic Cancer in the European Prospective Investigation into Cancer and Nutrition cohort

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Running head: Mediterranean Diet and pancreatic cancer risk in EPIC

Conflicts of interest

No potential conflicts of interest exist.

Abstract

Background: The Mediterranean Diet (MD) has been proposed as a means for cancer prevention, but little evidence has been accrued regarding its potential to prevent pancreatic cancer. We investigated the association between the adherence to the MD and pancreatic cancer risk within the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort.

Methods: Over half a million participants from 10 European countries were followed-up for over 11 years, after which 865 newly diagnosed exocrine pancreatic cancer cases were identified. Adherence to the MD was estimated through an adapted score without the alcohol component (arMED) to discount alcohol-related harmful effects. Cox proportional hazards regression models, stratified by age, sex and center, and adjusted for energy intake, body mass index (BMI), smoking status, alcohol intake and diabetes status at recruitment, were used to estimate hazard ratios (HRs) associated with pancreatic cancer and their corresponding 95% confidence intervals (CIs).

Results: Adherence to the arMED score was not associated with risk of pancreatic cancer (HR high *versus* low adherence = 0.99; 95% CI: 0.77-1.26, and HR per increments of 2 units in adherence to arMED = 1.00; 95% CI: 0.94-1.06). There was no convincing evidence for heterogeneity by smoking status, BMI, diabetes or European region. There was also no evidence of significant associations in analyses involving microscopically confirmed cases, plausible reporters of energy intake, or other definitions of the MD pattern.

Conclusion: A high adherence to the MD is not associated with pancreatic cancer risk in the EPIC study.

Keywords: Mediterranean diet, pancreatic cancer, cohort study

Introduction

Pancreatic cancer, of which pancreatic ductal adenocarcinoma (PDAC) is the most common type, is estimated to become the second leading cause of cancer-related death by 2030 in the US (Rahib *et al*, 2014). A trend of increasing mortality rates for pancreatic cancer is also foreseen in Europe (Malvezzi *et al*, 2015, Ferlay *et al*, 2016). The past decade has witnessed little therapeutic progress for this disease and obstacles to primary prevention persist on grounds of insufficient knowledge of the causative factors. In fact, only few risk factors of pancreatic cancer are well-established, namely smoking, non-O blood group, obesity, diabetes mellitus, heavy alcohol drinking and chronic pancreatitis (Maisonneuve & Lowenfels, 2015). The identification of additional risk factors is a challenge due to the complex and multi-factorial aetiology of pancreatic cancer. Dietary factors, which could be potentially modifiable, have not been consistently linked to pancreatic cancer (AICR/WCRF, 2012).

Results from numerous epidemiological studies support the hypothesis that the Mediterranean Diet (MD) is associated with a reduced cancer risk (Schwingshackl & Hoffmann, 2015; Couto *et al*, 2011, Benetou *et al*, 2008), as for example concerns breast (Buckland *et al*, 2013), colorectal (Bamia *et al*, 2013) and gastric cancers (Buckland *et al*, 2010). The underlying mechanisms by which the MD may exert this cancer-preventive effect are based on the inhibition of inflammatory, mutagenic and proliferative pathways in the carcinogenic process, and have been attributed to the synergistic interplay of various nutritional components, e.g. omega 6 and omega 3 fatty acids, fibre, antioxidants and polyphenols, provided by fruits, vegetables, legumes, olive oil and wine (Giacosa *et al*, 2013). There is, however, limited and inconsistent data on the association between *a priori*-defined scores of adherence to the MD and pancreatic cancer risk, with an Italian case-control study of nearly 700 pancreatic cancer cases reporting a significant inverse association (Bosetti *et al*, 2013a), and two prospective studies, one conducted in the US (n=1,057 cases) and another one in Sweden (n=92 cases), reporting conflicting results (Jiao *et al*, 2009; Tognon *et al*, 2012). The null results from the US study could be attributed to an overall lower adherence to the MD compared to European populations, whereas the sample size of the Swedish study undermines the reliability of a true inverse association between the MD and pancreatic cancer risk. Studies on *a posteriori*-defined MD patterns and their association with pancreatic cancer risk have also reported contradictory results (Nkondjock *et al*, 2005; Michaud *et al*, 2005; Chan *et al*, 2013; Inoue-Choi et al, 2011; Bosetti *et al*, 2013b). Therefore, it remains inconclusive whether an association between the MD and pancreatic cancer risk exists.

Despite the absence of a consistent pattern of association, a possible link between the MD and pancreatic cancer risk is supported by the fact that some dietary components of the MD have been associated individually with a reduced risk (e.g. fruits and vegetables) or increased risk (e.g. meat) of pancreatic cancer (Wu *et al*, 2016; Rohrmann *et al*, 2013). Further support for this association comes from the well-known MD and diabetes mellitus association. A high adherence to the MD as compared to a low adherence leads to a decreasing risk of diabetes mellitus (Koloverou *et al*, 2014; Romaguera *et al*, 2011), which could subsequently reduce the risk of pancreatic cancer owing to the causal link between both diseases. Thus, the MD could have a potential role in reducing pancreatic cancer risk through diabetes as a mediating factor in this relationship, or by being a common preventive factor of both diabetes and pancreatic cancer.

Our aim was to prospectively investigate the association between adherence to an *a priori*-defined MD index and pancreatic cancer risk. To this end we used a large European study population, featuring a wide range of variability in adherence to the MD across a North-South gradient, which also included Mediterranean populations.

Methods

Study population

EPIC is a multicenter prospective cohort study conducted in 23 centres in 10 European countries (Italy, France, Denmark, Germany, Greece, Spain, Norway, Sweden, United Kingdom, and The Netherlands). Over half a million participants (30% men) were recruited in the 1990s from the general population, except in some centers where other target populations were approached: breast cancer screening participants in Florence (Italy) and Utrecht (The Netherlands), mostly blood donors in Italy and Spain, vegetarian and health-conscious volunteers in Oxford (UK), and female members of the health insurance scheme for state school employees in France. EPIC was approved by the Internal Review Board of the International Agency for Research on Cancer (IARC), as well as by local institutions of the participating centers. All participants provided written informed consent. Methods of recruitment have been described in detail elsewhere (Riboli & Kaaks, 1997; Riboli *et al*, 2002).

We excluded a total of 23,785 participants with prevalent cancer at baseline other than non-melanoma skin cancer, 4,383 participants with missing or incomplete information on follow-up, 6,253 participants with incomplete dietary or non-dietary data, and 9,600 participants with a ratio for energy intake versus energy expenditure in the top or bottom 1%.The final study sample comprised 477,309 participants (29.8% men).

Pancreatic cancer cases ascertainment

Record linkage with population-based cancer registries and national mortality registries was performed to identify incident cancer cases and to assess the vital status of the participants. Complete follow-up data was obtained between 2004 and 2008 depending on the EPIC center. Active follow-up was carried out in Germany (up to 2008 for Potsdam and mid-2010 for Heidelberg), Greece (up to 2009), and France (up to 2006) by reviewing cancer, pathology and health insurance records of each participant, and also by directly contacting their next-of-kin. The mean duration of follow-up was 11.3 years.

Incident pancreatic cancer cases were defined as exocrine adenocarcinomas [International Classification of Diseases for Oncology, Third Edition (ICD-O-3), codes C25.0 - C25.3, C25.7 - C25.9]. Endocrine tumours (n = 40), secondary tumours (n = 67) and tumours of uncertain, benign or metastatic behaviour (n = 3) were all censored at the date of their diagnosis. We ended up with 865 pancreatic cancer cases, of which 608 cases (70.3%) were microscopically confirmed, based on histology of the primary tumour, histology of the metastasis, cytology or autopsy.

Assessment of diet and adherence to the MD

Participants were asked about their habitual diet over the previous year using country-specific validated dietary questionnaires (DQs) (Riboli *et al*, 2002), namely: quantitative food frequency questionnaires (FFQs) in Germany, Greece, Northern Italy and The Netherlands, diet history questionnaires in Spain, France and Ragusa (Italy), and semi-quantitative FFQs in Denmark, Naples (Italy), Norway, the UK (combined with a 7-day record) and Umeå (Sweden). In Malmö (Sweden), a quantitative FFQ and a 7-day food record with menu book to estimate portion sizes were used. The EPIC nutrient database (ENDB) was used to estimate nutrient and total energy intake from the DQs (Slimani *et al*, 2007).

The relative Mediterranean diet score (rMED), as previously applied in other EPIC studies (Buckland *et al*, 2010; Buckland *et al*, 2013) and similar in concept to the original mediterranean diet score (Trichopoulou *et al*, 2003), was used to estimate level of conformity to the MD. It is an 18-point scale that incorporates 9 selected components of the MD. Each component was calculated as a function of energy density (g/1000kcal/day), using the nutrient density model (Willet *el al*, 1997), and then divided into country-specific tertiles of intakes (except for olive oil). For the 6 components presumed to fit the MD; fruits (including nuts and seeds), vegetables (excluding potatoes), legumes, fish (including seafood), olive oil and cereals (white and nonwhite), a score of 0 to 2 points was assigned to the 1st (0 points), 2nd (1 point) and 3rd (2 points) tertile of intake, respectively. The scoring scheme for olive oil consisted of assigning 0 points to non-consumers, 1 point for participants below the median of intake and 2 points for levels of intake equal or above this median. For the 2 components presumed not to fit MD, meat (including meat products) and dairy products, the scoring was reversed (1st, 2nd and 3rd tertile: 2, 1 and 0 points, respectively). Because alcohol consumption has been potentially associated with pancreatic cancer (Maisonneuve & Lowenfels, 2015), the alcohol component (the 9th component) was removed from the score and the non-alcohol MD score (arMED) was used instead (Buckland *et al*, 2013). Thus, the range of the arMED score contained 8 components and the point scale ranks from 0-16, whereby 0 represents the lowest adherence to the MD pattern and 16 the highest adherence. The arMED score was further classified into low (0–5 points), medium (6–9 points), or high (10–16 points) adherence levels based on of previously published cutoff points (Buckland *et al*, 2013).

Lifestyle data

Standardized questionnaires were used to collect lifestyle data at recruitment including self-reported diabetes status, history of smoking and alcohol consumption, physical activity and socio-economic status. Diagnosis of diabetes of about half of all self-reported cases was confirmed through linkage to diabetes mellitus registries, patient records, or using other procedures (Nöthlings *et al*, 2011). Height and weight were measured in all EPIC centers except in Norway, France and in a subgroup of the Oxford cohort where these data were self-reported. Anthropometric measurements also included waist circumference, except in Norway, in Umeå and in Oxford where only self-reported data were collected (Riboli *et al*, 2002). Measurements were corrected for differences in clothing and self-reported data of the aforementioned centers were corrected using prediction equations based on a fraction of real measurements (Haftenberger *et al*, 2002).

Statistical analysis

Cox proportional hazards regression models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for adherence to the arMED score associated with pancreatic cancer risk. Regression models were stratified by age at recruitment in 1-year categories, sex and center to control for between-center differences in the dietary assessment methods used at recruitment and differences in follow-up procedures. Time at entry was age at recruitment, and time at exit was age at first pancreatic cancer diagnosis for cases and age at censoring for non-cases (death, loss to follow-up, or end of the follow-up, whichever came first). The proportional hazard assumption was satisfied in all models as indicated by the plots of Schoenfeld residuals on functions of time (Schoenfeld, 1982).

Adherence to the arMED was modelled as a categorical variable by dividing the score into low, medium and high levels of adherence. The low adherence category was considered as the referent group. The trend of association across levels of adherence was evaluated by using a linear variable of the medians of the score in each stratum.

Adherence to the arMED was also modelled on a continuous scale to estimate risks associated per increments of two units in the adherence. Restricted cubic splines functions in models of three and four knots on the distribution of the arMED score, to evaluate the shape of the dose-response relationship between the arMED and pancreatic cancer risk (Heinzl & Kaider, 1997), suggested a linear relationship.

Covariates considered *a priori* as factors known or suspected to be associated with pancreatic cancer risk and the MD were tested for confounding by comparing models with and without each variable. Those variables that changed estimates by more than 10% were retained in the regression model. Physical activity and educational level did not comply with these criteria. Risk estimates for models with waist circumference or body mass index (BMI) did not substantially differ. The association of adherence to the arMED score with pancreatic cancer risk was examined in crude models (stratified by age, sex, and center), and in multivariate models (additionally adjusted for energy intake, BMI, smoking status, alcohol intake, and diabetes status).

The modifying effect of sex, BMI (normal, overweight and obese, according to WHO criteria), waist circumference (normal/moderate and large, according to NCEP/ATPIII criteria, 2002), physical activity (active and non-active) to elucidate further the potential effect-measure modification of overweight and obesity, smoking status (never, former and current smoker), median age at recruitment (< 60 and ≥ 60 years) and alcohol consumption (abstainers, moderate drinkers and drinkers, equivalent to 0 g/day, ≤ 12 g/day or > 12 g/day alcohol use, respectively) was evaluated through stratified analyses and the likelihood ratio test statistic in regression models with and without multiplicative interaction terms between these variables and the arMED score. In addition, we considered the influence of smoking duration and intensity on the arMED and pancreatic cancer risk association in current and former smokers. Heterogeneity by country and region (Southern, Central and Northern Europe) was also assessed by introducing an interaction term between countries/regions and the arMED score in the model.

The possible mediating effect of diabetes mellitus on this association was further evaluated in two different scenarios using mediation analysis (Tingley *et al*, 2014): i) a direct effect of the arMED score on pancreatic cancer risk; and ii) an indirect effect with diabetes mellitus as an intermediate in the causal pathway. A logistic regression model of the arMED score on diabetes status at baseline, followed by a hazard model to the onset of pancreatic cancer including arMED and the same covariates as well as the mediator variable (diabetes status) were fitted to estimate the average direct (ADE) and the average causal mediation effect (ACME) of diabetes.

Sensitivity analyses were performed by the exclusion of cases diagnosed within the first two years of follow-up (88 cases) to evaluate the influence of early effects of subclinical disease on the associations as well as those occurred within the first five years of follow-up (258 cases) to account for another time point of disease progression. We also excluded (i.e. censored) non-microscopically confirmed cases (257 cases) to minimize possible misclassification of tumours. Analyses were further restricted to 523 confirmed cases belonging to the pancreatic ductal adenocarcinoma (PDAC) histological subtype. HRs of pancreatic cancer associated with adherence to the arMED score were compared with the score including alcohol as an additional component, i.e. the original rMED score (Buckland *et al*, 2010). Alcohol was scored dichotomously assigning 2 for moderate consumption (sex-specific cutoff points: 5-25 g/day for women and 10-50 g/day for men) and 0 for intakes outside this range. Other sensitivity analyses included the comparison of HRs estimated using cohort-wide tertiles, the Mediterranean Diet Scale (MDS) (Trichopoulou *et al*, 2003) and the Mediterranean Dietary Pattern MDP scores (Sánchez-Villegas *et al*, 2006). Analyses excluding misreporters of energy intake, as defined by Goldberg (under-repoters if ratio of energy intake:basal metabolic rate -EI:BMR <1.14 and over-reporters if EI:BMR >2.1), were also conducted (Goldberg *et al*, 1991). In addition, each dietary component of the MD score was subtracted one at a time from the arMED score to investigate whether the removed component changed the risk estimates with respect to the regression models of the complete arMED score.

Statistical software used for the data analysis were Stata 12.0 (College Station, TX: Stata Corp LP, 2005) and R 3.2.1. Statistical significance was based on two-sided p values < 0.05.

Results

The arMED score ranged between 4 and 11.3 points (mean score: 7.81 ± 2.63). Mean overall adherence to the arMED score was higher in Southern European countries than in Northern European countries, except in the UK (possibly driven by the vegetarian and health-conscious participants of the Oxford subcohort) (Supplemental Table 1). According to the participants' demographic and lifestyle characteristics, higher levels of adherence to the arMED score were more frequent among those who were younger, less educated, non-smokers, physically inactive or obese. Participants with self-reported diabetes mellitus at baseline also showed a higher adherence level to this dietary pattern probably as a result of adopting healthier dietary habits to manage their disease. Intakes of nutrient antioxidants, fiber, plant-based food and olive oil were higher in the high adherence group, while that of dairy products and meats was lowest (Table 1).

Table 2 shows HR estimates of adherence to the arMED score associated with pancreatic cancer risk, overall and by subgroups. Compared to a low level of adherence to the arMED score, a higher adherence was not associated with risk of pancreatic cancer, either in the minimally-adjusted (HR = 0.88; 95% CI: 0.69-1.12; *p-trend* = 0.24), or multivariate-adjusted models (HR = 0.99; 95% CI: 0.77-1.26; *p*-trend = 0.95). HRs associated to increments of 2 units in the adherence to the arMED score did also not reach statistical significance (HR = 1.00; 95% CI: 0.94-1.06).

No indication for effect modification by BMI, age, smoking status, sex, physical activity, alcohol status, and abdominal obesity was apparent (*p-value* for interaction = 0.43, 0.59, 0.56, 0.90, 0.46, 0.20, 0,76, respectively). There was also no evidence for interaction by diabetes status (*p-value* = 0.11). HRs for pancreatic cancer per 2 units increment in arMED in non-diabetics tended to be inversely associated with pancreatic cancer risk in crude models (HR = 0.97; 95% CI: 0.94-1.00), but not after adjusting for smoking in the multivariate-adjusted model (HR = 0.98; 95% CI: 0.91-1.04). No such inverse pattern of association was observed in the subset of diabetics, although a relatively small number of pancreatic cancer cases (n=55) were available for this analysis (data not shown). Results of the mediation analysis also did not support a mediating effect of diabetes on this association (ACME *p-value* = 0.90, ADE *p-value* = 0.02).

Stratified analyses by country or European region did not reveal statistically significant heterogeneity between strata for the association between adherence to the arMED score with pancreatic cancer risk (*p-value* = 0.62 and 0.11, respectively). A borderline inverse association in the Southern European cohort was observed, yet without reaching statistical significance (HR per 2 unit increment in arMED = 0.88; 95% CI: 0.76-1.03, *p-value* = 0.07).

Results of the sensitivity analyses are shown in Table 3 and Supplemental Table 2. HRs remained virtually the same in analyses restricted to microscopically confirmed cases or to participants with a follow-up longer than 2 years or 5 years. No differences in the associations were further observed for PDAC tumours. The distribution of participants by the arMED score either defined as country-specific or cohort-wide tertiles was similar (23.1%, 46.7%, 29.4% and 24.2%, 45.3%, 30.5%, respectively) and HR estimates did not appreciably change when cohort-wide tertiles of the arMED score were used as the exposure of interest variable. We did also not observe any variations in risk estimates when considering adherence to the rMED score, i.e. the score including alcohol, instead. The same was true for the other MD scores (MDS and MDP), with or without the contribution of alcohol to the scores. Estimates of HRs in the study population of valid reporters of energy intake did also not reach the level of statistical significance (HR per 2 unit increments in arMED = 0.95; 95% CI: 0.88-1.03). Furthermore, no differences in risk estimates were seen after removing each arMED component of the score (Table 3). In addition, none of these components was individually associated with pancreatic cancer risk in multivariate adjusted models controlling for the remaining components (data not shown).

Discussion

Risk of pancreatic cancer was not associated with adherence to a non-alcohol defined MD score (arMED) in this large European prospective cohort study, nor was there any evidence of a significant association between the arMED score and pancreatic cancer risk in stratified analyses by diabetes, smoking, BMI or European region.

Few studies have examined the association between adherence to the MD and pancreatic cancer risk. The National Institutes of Health-AARP Diet and Health Study (NIH-AARP) prospectively evaluated this association in a diabetes-free study population including 1,057 pancreatic cancer cases (Jiao *et al*, 2009). In this study, adherence to the MD was considered as part of a healthy lifestyle score, which also included tobacco and alcohol consumption, BMI and physical activity. The MD score was derived from the MDS (Trichopoulou *et al*, 2003), but was further adapted by removing the alcohol component. The risk of pancreatic cancer was significantly lower in participants who scored highest compared to those in the group of lowest compliance with the lifestyle score (RR = 0.42; 95% CI: 0.26–0.66). The independent effect of the MD score on pancreatic cancer risk was also evaluated in this study, but a non-statistically significant 8% (95% CI 0.81-1.05) reduced pancreatic cancer risk was seen when a high *versus* a low non-alcohol MD adherence was compared, indicating that a healthy dietary pattern, such as the MD, may not have the capacity on its own to reduce risk of pancreatic cancer. Interestingly, nonsmoking (never or former smokers who quit smoking for 10 or more years) and normal weight (BMI < 25 kg/m^2) were the only two features of the lifestyle score independently associated with a decreased pancreatic cancer risk. Nonsmoking yielded the greatest risk reduction within the score (RR = non-smokers *versus* smokers = 0.59; 95% CI: 0.51-0.67). Therefore, the pancreatic cancer risk-reducing effect of this lifestyle score could be entirely attributed to the smoking component. In support of this argument, a cross-comparison of smoking status and levels of adherence to the arMED score in our study revealed that non-smokers, defined likewise as never or long-term former smokers (≥ 10 years), with a high adherence to the arMED score as compared to current smokers or early former smokers with a low adherence to the arMED score had a 42% (95% CI: 0.43-0.78) lower risk of pancreatic cancer.

Another prospective study addressing the association between adherence to the MD (defined as the MDS, with some modifications) and pancreatic cancer mortality reported a 28% reduction in mortality (though, statistically significant only in men: 95% CI: 0.68-0.99) for high versus low adherence to the MD score (Tognon *et al*, 2012). This study included only 92 pancreatic cancer cases, which were ascertained in Sweden among the 77,151 participants of the Västerbotten Intervention Program study. Residual confounding and selection bias (subjects with higher mortality risk were excluded) prevent direct comparison of their results with those obtained in our study. The only study reporting a significant association between the MD (the MDS) and

pancreatic cancer is an Italian case-control study that included 688 cases and 2,204 hospital-based controls. In this study, risk of pancreatic cancer decreased by 15% (95% CI: 0.80-0.91) per one unit increment in the adherence to the MD (Bosetti *et al*, 2013). This association was consistent across strata of age, BMI, alcohol and smoking status, and was stronger in non-diabetics (OR = 0.84) as compared to diabetics (OR=0.99; *p-value* for interaction: 0.01). In our study, high versus low adherence to the arMED score also pointed to a stronger, though non-statistically significant, inverse association between the MD and pancreatic cancer risk in non-diabetics (HR=0.91; 95% CI: 0.70-1.19). We could not examine the association in diabetics because only 55 of them developed pancreatic cancer during follow-up, but we did not observe any evidence for effect modification by diabetes status. The other prospective studies did not assess how MD is associated with pancreatic cancer risk in diabetics as compared to non-diabetics. Although the number of diabetics with pancreatic cancer was limited in number in our study population, our results suggest that diabetes status does not mediate any possible association between the MD and pancreatic cancer risk.
Finally, a recently published meta-analysis on the adherence to the MD and cancer incidence and mortality concluded for pancreatic cancer that a high adherence to this dietary pattern leads to a statistically non-significant reduced risk (RR = 0.64; 95% CI: 0.38-1.08) when compared to a low adherence (Schwingshackl & Hoffmann G, 2014). However, this reported risk estimate was not derived from all available published studies on this association; only estimates of the Italian and Swedish studies were pooled.

All of these earlier studies exploring the association between the MD and pancreatic cancer risk are prone to misclassification of the outcome (data for histologically confirmed cases were not provided), and some of them did not account for implausible reporting of dietary intake on the basis of estimated energy requirements to rule out exposure misclassification. Selection bias, although less likely present in cohort studies, might be another issue. Also, MD patterns in American and Nordic populations might not adequately reflect the traditional MD pattern. In our study, the association was, indeed, to some extent stronger in Southern European countries, though it still did not reach statistical significance. Thus, our results seem to indicate that adherence to the MD does not reduce pancreatic cancer risk.

Similarly, two prospective studies assessing *a-posteriori* defined MD-like dietary patterns reported no association with pancreatic cancer risk (Michaud *et al*, 2005; Inoue-Choi et al, 2011). Also, neither single dietary components of the MD nor the combination of them in the arMED score appeared to be linked to pancreatic cancer risk in our study. In addition, we rendered similar risk estimates after considering the traditional rMED score that includes the alcohol component (Buckland *et al*, 2010). Overall, evidence supporting a role of dietary factors commonly supplied by the MD (antioxidant-rich foods, such as fruits and vegetables, and limited intake of red meat) for the prevention of this disease is still sparse (AICR/WCRF, 2012, Koushik *et al*, 2012; Larsson *et al*, 2012; Vrieling *et al*, 2009; Rohrmann *et al*, 2013).

Several limitations of this study should be considered. Our results rely on dietary data measured at a single time point which would not reflect longitudinal changes in dietary intake. Residual confounding might be present as we were unable to control for all known risk factors of pancreatic cancer, such as family history of pancreatic cancer, or for other putative factors potentially associated with pancreatic cancer risk. Confounding by smoking might be also an issue, despite the fact that additionally controlling for smoking duration and intensity did not substantially affect our results. Diabetes mellitus status could have biased our results due to misclassification, but neither self-reported nor validated data on type 2 diabetes mellitus status at baseline made a substantial difference.

Strengths of our study are its prospective nature, as well as the large sample size and long follow-up, which enabled us to conduct stratified analysis by potential effect modifiers with sufficient statistical power. Also, we were able to minimize bias due to misclassification of the outcome after restricting the study population to microscopically confirmed cases, and could confirm absence of any influence of pre-diagnostic disease on the association. Moreover, our results remained unchanged at different follow-up time points. We excluded misreporters of energy intake to ensure that reporting bias did not influence our results. However, as in any other diet-cancer association study, dietary measurement error cannot be dismissed. Our results also rely on a MD score that has been widely used in diet-cancer risk-association studies, in which the utility of the MD for the primary prevention of various cancer sites was demonstrated (Buckland *et al*, 2010, 2013; Bamia *et al*, 2013). Moreover, our study addresses the MD-pancreatic cancer risk association, for the first time, in a large European population that includes countries from the Mediterranean regions, accounting for a wide range of adherence to the MD pattern.

In conclusion, results of our study, conducted within the prospective EPIC cohort, suggest that adherence to the MD is not associated with the development of pancreatic cancer.

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Tables:

Table 1: Baseline characteristics of the EPIC cohort (n = 477,309) according to adherence to the arMED score.

Table 2: Hazard ratios (95% confidence intervals) of pancreatic cancer by country-specific levels of adherence to the arMED score in the EPIC cohort (n = 477,309).

Table 3: Hazard ratios (HRs) and 95% confidence intervals (CIs) of pancreatic cancer associated with the arMED score in the EPIC cohort (n = 477,309) after removing score components one at a time.

Supplemental Tables:

Supplemental Table 1: Description of the EPIC cohort (n = 477,309) by country, sex, distribution of pancreatic cancer cases and adherence to the arMED score.

Supplemental Table 2: Hazard ratios (95% confidence intervals) of pancreatic cancer by levels of adherence to the arMED score regarding sensitivity analyses in the EPIC cohort (n = 477,309).

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Supplemental Table 1: Description of the EPIC cohort (n = 477,309) by country, sex, distribution of pancreatic cancer cases and adherence to the arMED score

	Age, years median (IQR)	Cases (n)	microscopically confirmed (n)	Cohort sample (n)	Pers-years	Mediterranean Diet arMED score, mean (sd) Low: 0-5	Medium: 6-9	High: 10-16
Men								
Italy	49.7 (44.2 - 76.3)	27	20	14,029	158,917	4.67 (0.64)	7.99 (0.98)	10.93 (1.07)
Spain	49.9 (44.6 - 56.5)	28	23	15,148	182,965	4.58 (0.68)	8.07 (0.98)	11.73 (1.45)
UK	52.9 (43.9 - 63.7)	51	9	22,851	252,096	4.21 (0.97)	7.52 (1.10)	11.14 (1.10)
The Netherlands	43.9 (34.6 - 52.1)	15	15	9,639	115,570	3.95 (1.05)	6.85 (0.95)	10.52 (0.82)
Greece	52.0 (42.1 - 64.1)	20	10	10,807	99,108	4.43 (0.85)	8.42 (0.79)	11.65 (1.35)
Germany	53.0 (45.8 - 58.7)	64	48	21,172	208,509	4.06 (1.01)	7.00 (1.00)	10.59 (0.83)
Sweden	51.4 (40.7 - 60.1)	73	73	22,309	289,623	3.65 (1.20)	6.84 (0.94)	10.52 (0.86)
Denmark	56.0 (52.7 - 60.2)	118	110	26,294	284,721	3.74 (1.18)	7.05 (1.03)	10.77 (1.02)
All	52.2 (45.7 - 59.6)	396	308	142,249	1,591,508	3.85 (1.14)	7.35 (1.11)	11.37 (1.32)
Women								
France	51.5 (47.0 - 57.4)	46	18	67,385	699,360	4.33 (0.91)	7.64 (1.08)	11.04 (1.17)
Italy	50.9 (44.4 - 56.7)	41	25	30,512	341,489	4.63 (0.64)	7.94 (1.01)	11.43 (1.37)
Spain	47.7 (41.3 - 54.9)	31	23	24,854	299,617	4.48 (0.79)	8.07 (0.99)	11.72 (1.43)
UK	47.9 (36.4 - 57.9)	72	10	52,543	586,301	4.35 (0.89)	7.81 (1.07)	11.27 (1.17)
The Netherlands	52.7 (46.0 - 58.9)	52	32	26,866	315,683	4.07 (1.01)	7.10 (1.04)	10.67 (0.92)
Greece	53.6 (43.1 - 63.9)	16	5	15,225	148,604	4.90 (0.31)	8.44 (0.77)	11.60 (1.32)
Germany	48.4 (41.1 - 57.0)	41	26	27,411	272,105	4.06 (1.02)	7.18 (1.05)	10.68 (0.92)
Sweden	50.6 (46.7 - 60.1)	79	77	26,374	349,308	3.94 (1.11)	7.13 (1.03)	10.57 (0.86)
Denmark	56.3 (52.8 - 60.4)	71	65	28,722	316,745	4.09 (1.03)	7.31 (1.07)	10.94 (1.12)
Norway	48.0 (44.3 - 51.8)	20	19	35,168	342,279	4.42 (0.82)	7.50 (1.07)	10.63 (0.82)
All	50.8 (44.9 - 57.5)	469	300	335,060	3,671,490	4.14 (1.01)	7.54 (1.10)	11.28 (1.28)

The cohorts from France, Norway, Naples (Italy) and Utrecht (the Netherlands) were comprised of women only.
Distribution of participants (%) by country and arMED score (Low, Medium, High): France (25.2, 53.5, 21.3), Italy (10.1, 51.3, 38.5), Spain (14.4, 53.3, 32.3), UK (24.6, 47.2, 28.3), The Netherlands (28.6, 53.8, 17.1), Greece (11.4, 52.5, 36.1), Germany (20.1, 53.5, 26.4), Sweden (34.8, 54.0, 11.2), Denmark (28.2, 46.9, 24.1), Norway (42.4, 48.6, 9.0)

Supplemental Table 2: Hazard ratios (95% confidence intervals) of pancreatic cancer by levels of adherence to the arMED score regarding sensitivity analyses in the EPIC cohort (n = 477,309).

	arMED Score				per 2 unit increment in arMED score
	Low (0-5) HR (95% CI)	Medium (5-9) HR (95% CI)	High (10-16) HR (95% CI)	*P-value* for trend	HR (95% CI)
Microscopically confirmed (n=608 cases)					
Cases/person-years	232/1,244,895	281/2,482,870	95/1,533,440		
HR (95% CI)	1.00	1.01 (0.84-1.22)	0.88 (0.64-1.21)	0.60	1.00 (0.92-1.07)
PDAC (n = 523 cases)					
Cases/person-years	194/1,215,106	251/2,322,715	78/1,498,017		
HR (95% CI)	1.00	1.10 (0.90-1.34)	1.02 (0.73-1.43)	0.65	1.04 (0.96-1.12)
> 2 years follow-up (n=777 cases)					
Cases/person-years	249/1,242,826	356/2,479,370	172/1,532,026		
HR (95% CI)	1.00	1.01 (0.85-1.20)	1.05 (0.81-1.36)	0.72	1.01 (0.95-1.08)
> 5 years follow-up (n=607 cases)					
Cases/person-years	195/1,227,903	281/2,450,723	131/1,512,027		
HR (95% CI)	1.00	1.04 (0.85-1.26)	1.04 (0.77-1.39)	0.77	1.03 (0.95-1.11)
Score with alcohol or cohort-wide tertiles					
rMED (arMED with alcohol) (n=865 cases)					
Cases/person-years	238/1,285,576	416/2,696,589	211/1,280,834		
HR (95% CI)	1.00	0.96 (0.81-1.14)	1.12 (0.95-1.46)	0.15	1.02 (0.97-1.08)
arMED cohort-wide (n=865 cases)					
Cases/person-years	287/1,316,756	387/2,365,824	191/1,580,418		
HR (95% CI)	1.00	1.08 (0.91-1.28)	1.03 (0.80-1.33)	0.95	1.00 (0.94-1.07)
Other scores of adherence to the MD					
MDS index (n=865 cases)					
Cases/person-years	169/836,692	496/2,955,606	200/1,470,700		
HR (95% CI)	1.00	1.01 (0.84-1.21)	1.05 (0.81-1.35)	0.73	1.01 (0.96-1.06)
MDS index without alcohol (n=865 cases)					
Cases/person-years	226/1,121,521	499/3,056,350	140/1,085,128		
HR (95% CI)	1.00	1.03 (0.87-1.22)	1.01 (0.78-1.32)	0.67	1.01 (0.91-1.12)
MDP index (865 cases)					
Cases/person-years	400/1,832,886	295/1,901,566	170/1,528,546		
HR (95% CI)	1.00	1.03 (0.87-1.21)	0.90 (0.70-1.14)	0.52	1.00 (0.94-1.07)
MDP index without alcohol (n=865 cases)					
Cases/person-years	499/2,420,101	189/1,258,293	177/1,584,604		
HR (95% CI)	1.00	1.06 (0.88-1.28)	0.91 (0.71-1.14)	0.57	1.01 (0.94-1.08)
Excluding misreporters of energy intake (n=565 cases)					
Cases/person-years	191/839,247	263/1,622,623	111/1,008,312		
HR (95% CI)	1.00	0.98 (0.80-1.20)	0.80 (0.58-1.10)	0.22	0.95 (0.88-1.03)

Multivariate HRs - adjusted for total energy intake (continuous), body mass index (continuous), smoking status and intensity (never; current , 1-15 cigarettes per day; current, 16-25 cigarettes per day; current, 26+ cigarettes per day; former, quit ≤10 years; former, quit 11-20 years; former, quit 20+ years; current, pipe/cigar/occasional; current/former, missing; unknown), alcohol intake (non-drinkers, drinkers of 0-6 g/d, >6-12 g/d, >12-24g/d, >24-60 g/d, women drinkers of: >60g/d, men drinkers of: >60-96 g/d, >96 g/d), diabetes (verified, not verified but self-reported, not diabetes, missing), and stratified by age (1-year categories), sex, and centre.

Table 1. Baseline characteristics of the EPIC cohort (n = 477,309) according to adherence to the arMED score.

Characteristics	arMED score in Men			arMED score in Women		
	Low (0-5)	Medium (6-9)	High (10-16)	Low (0-5)	Medium (6-9)	High (10-16)
Adherence arMED (mean ± SD)	3.85 (1.14)	7.35 (1.11)	11.37 (1.32)	4.14 (1.01)	7.54 (1.10)	11.28 (1.28)
Age, years (mean ± SD)	52.3 ± 9.9	52.6 ± 10.0	51.2 ± 10.6	51.4 ± 9.7	51.2 ± 9.3	49.8 ± 10.6
Education ≥ secondary school, n (%)	32,690 (66.1)	39,000 (66.6)	18,781 (54.9)	41,981 (69.3)	119,520 (71.0)	65,328 (61.6)
Weight, kg (mean ± SD)	82.0 ± 12.4	80.7 ± 11.8	79.4 ± 11.6	67.2 ± 12.3	65.5 ± 11.5	65.0 ± 11.4
BMI, kg/m² (mean ± SD)	26.3 ± 3.6	26.4 ± 3.6	27.0 ± 3.8	25.1 ± 4.4	24.7 ± 4.2	25.2 ± 4.6
Obese (≥30kg/m²), n (%)	6,926 (14.0)	8,278 (14.1)	6,596 (19.3)	7,780 (12.9)	18,547 (11.0)	15,912 (15.0)
Waist circumference, cm (mean ± SD)	95.0 ± 10.4	94.0 ± 10.0	95.2 ± 10.2	81.0 ± 11.4	79.6 ± 11.0	80.3 ± 11.9
≥ 102 cm in men or ≥ 88 cm in women, n (%)	9,832 (19.9)	11,232 (19.2)	8,601 (25.1)	11,022 (18.2)	23,151 (13.8)	21,266 (20.1)
Physical Activity > moderate active, n (%)	24,329 (49.2)	28,274 (48.3)	16,315 (47.7)	24,169 (39.9)	59,685 (35.4)	34,380 (32.4)
Current smoker, n (%)	16,269 (32.9)	15,779 (26.9)	9,758 (28.5)	17,069 (28.2)	32,311 (19.2)	15,903 (15.0)
Alcohol intake, median g (IQR)	12.1 (4.1-29.2)	13.8 (4.8-30.7)	13.04 (3.4-29.8)	3.8 (0.8-11.4)	3.9 (0.8-11.6)	2.8 (0.4-10.2)
Heavy intake (≥ 96 g/d in men or ≥ 60 g/d in women), n (%)	3,623 (7.3)	3,853 (6.6)	1,887 (5.5)	637 (1.1)	1,178 (0.7)	361 (0.3)
Dietary intake						
Total energy intake, kcal (mean ± SD)	2470 ± 665	2391 ± 657	2356 ± 660	1956 ± 533	1929 ± 543	1921 ± 539
Carbohydrate, g (mean ± SD)	261.4 ± 80.6	259.5 ± 82.4	250.7 ± 79.9	211.0 ± 65.6	213.8 ± 66.6	219.7 ± 69.1
Fat, g (mean ± SD)	98.7 ± 33.0	91.0 ± 31.4	91.8 ± 33.2	79.7 ± 26.7	75.7 ± 26.9	74.4 ± 26.8
Saturated Fat, g (mean ± SD)	41.2 ± 14.8	34.6 ± 13.0	28.2 ± 11.3	33.9 ± 12.4	30.1 ± 11.8	25.7 ± 10.6
Vitamin C, mg (mean ± SD)	96.5 ± 52.1	121.9 ± 67.3	158.5 ± 88.6	100.7 ± 54.7	128.9 ± 65.5	154.5 ± 73.8
Vitamin E, mg (mean ± SD)	11.7 ± 6.0	13.3 ± 6.4	14.7 ± 6.7	10.8 ± 5.2	11.8 ± 5.4	12.6 ± 5.4
Beta-Carotene, ug (mean ± SD)	2327.3 ± 1980.6	3080.5 ± 2589.8	4062.6 ± 3284.8	2917.0 ± 2086.0	3735.4 ± 2668.0	4660.2 ± 3591.7
Folate, ug (mean ± SD)	285.7 ± 90.4	313.6 ± 109.1	376.5 ± 139.9	254.2 ± 87.2	293.2 ± 109.9	348.6 ± 37.6
Fiber, g (mean ± SD)	21.5 ± 7.3	24.5 ± 8.0	28.0 ± 8.9	18.5 ± 5.9	21.6 ± 6.5	25.1 ± 8.0
Meat & Meat products, g (mean ± SD)	148.6 ± 69.0	120.9 ± 65.4	96.6 ± 65.7	109.0 ± 49.8	92.0 ± 50.6	67.8 ± 48.3
Dairy products, g (mean ± SD)	450.8 ± 321.0	311.0 ± 225.3	214.9 ± 164.6	434.4 ± 263.4	329.9 ± 211.2	245.7 ± 172.0
Fruit, nuts & Vegetables, g (mean ± SD)	234.8 ± 131.0	387.6 ± 218.9	693.4 ± 323.5	278.3 ± 151.4	431.4 ± 223.8	637.4 ± 282.7
Cereals, g (mean ± SD)	214.0 ± 95.6	269.7 ± 135.6	295.0 ± 135.8	162.8 ± 71.0	197.5 ± 93.5	235.5 ± 109.7
Legumes, g (mean ± SD)	4.4 ± 10.6	14.3 ± 26.5	35.9 ± 36.6	4.2 ± 9.6	10.3 ± 17.2	25.3 ± 25.8
Fish, g (mean ± SD)	27.5 ± 25.6	36.5± 32.0	48.6 ± 43.9	24.6 ± 28.1	38.7 ± 37.5	43.4 ± 37.4
Olive Oil, g (mean ± SD)	0.4 ± 2.3	7.0 ± 14.0	26.1 ± 23.5	0.5 ± 2.4	3.6 ± 9.2	12.6 ± 17.1
Diabetes, yes (self-reported), n (%)	1,309 (2.7)	2,219 (3.8)	1,572 (4.6)	1,090 (1.8)	3,440 (2.0)	2,902 (2.7)

All dietary intakes are estimated from the FFQ and not energy-adjusted.
Missing data on Educational level for 1,260 men and 4,964 women; Physical activity for 3,075 men and 38,956 women; Waist circumference for 12,043 men and 94,998 women; Smoking status for 1,959 men and 7,774 women; Diabetes status at recruitment for 3,096 men and 13,745 women.

Table 2: Hazard ratios (95% confidence intervals) of pancreatic cancer by country-specific levels of adherence to the arMED score in the EPIC cohort (n = 477,309).

	arMED Score				per 2 unit increment in arMED score
	Low (0-5) HR (95% CI)	Medium (6-9) HR (95% CI)	High (10-16) HR (95% CI)	*P-value* for trend	HR (95% CI)
All *(n=865 cases)*					
Cases/person-years	277/1,245,196	402/2,483,735	186/1,534,067		
Crude HR (95% CI)	1.00	0.94 (0.80-1.11)	0.88 (0.69-1.12)	0.24	0.98 (0.95-1.01)
Multivariate HR (95% CI)	1.00	1.01 (0.85-1.19)	0.99 (0.77-1.26)	0.95	1.00 (0.94-1.06)
Men *(n=396 cases)*					*P*-value for interaction: 0.90
Cases/person-years	165/565,143	160/649,987	71/376,379		
Crude HR (95% CI)	1.00	0.92 (0.73-1.16)	0.88 (0.59-1.30)	0.45	0.97 (0.88-1.06)
Multivariate HR (95% CI)	1.00	0.99 (0.78-1.25)	1.00 (0.68-1.49)	0.99	1.01 (0.92-1.11)
Women *(n=469 cases)*					
Cases/person-years	112/680,053	242/1,833,748	115/1,157,688		
Crude HR (95% CI)	1.00	0.96 (0.76-1.21)	0.89 (0.65-1.22)	0.46	0.96 (0.88-1.04)
Multivariate HR (95% CI)	1.00	1.03 (0.82-1.31)	0.99 (0.72-1.37)	0.98	0.99 (0.91-1.08)
Age < 60 years *(n=486 cases)*					*P*-value for interaction: 0.59
Cases/person-years	168/965,742	225/1,970,708	93/1,249,488		
Crude HR (95% CI)	1.00	0.88 (0.71-1.09)	0.71 (0.51-0.98)	0.04	0.94 (0.87-1.03)
Multivariate HR (95% CI)	1.00	0.95 (0.76-1.18)	0.80 (0.58-1.12)	0.23	0.98 (0.90-1.07)
Age ≥ 60 years *(n=379 cases)*					
Cases/person-years	109/279,454	177/513,027	93/284,579		
Crude HR (95% CI)	1.00	1.03 (0.80-1.33)	1.16 (0.80-1.67)	0.46	0.99 (0.89-1.08)
Multivariate HR (95% CI)	1.00	1.10 (0.85-1.41)	1.30 (0.89-1.87)	0.18	1.02 (0.92-1.12)
Never smoker *(n=336 cases)*					*P*-value for interaction: 0.56
Cases/person-years	81/518,518	169/1,229,294	86/847,954		
Crude HR (95% CI)	1.00	1.02 (0.77-1.36)	0.91 (0.62-1.34)	0.65	0.98 (0.88-1.08)
Multivariate HR (95% CI)	1.00	1.03 (0.77-1.37)	0.92 (0.63-1.37)	0.71	0.98 (0.89-1.09)
Former smoker *(n=239 cases)*					
Cases/person-years	68/340,265	115/681,518	56/376,769		
Crude HR (95% CI)	1.00	1.13 (0.83-1.55)	1.35 (0.87-2.12)	0.19	1.03 (0.92-1.16)
Multivariate HR (95% CI)	1.00	1.15 (0.83-1.57)	1.42 (0.91-2.22)	0.13	1.05 (0.93-1.18)
Smoker *(n=247 cases)*					
Cases/person-years	126/371,157	109/519,272	40/278,996		
Crude HR (95% CI)	1.00	0.84 (0.64-1.12)	0.66 (0.40-1.08)	0.09	0.94 (0.84-1.05)
Multivariate HR (95% CI)	1.00	0.86 (0.65-1.14)	0.67 (0.41-1.11)	0.11	0.95 (0.85-1.06)
Non-Diabetics *(n=776 cases)*					*P*-value for interaction: 0.11
Cases/person-years	259/1,174,297	355/2,321,163	162/1,448,174		
Crude HR (95% CI)	1.00	0.89 (0.75-1.05)	0.81 (0.63-1.05)	0.09	0.97 (0.94-1.00)
Multivariate HR (95% CI)	1.00	0.95 (0.80-1.13)	0.91 (0.70-1.19)	0.48	0.98 (0.91-1.04)
‡ ***Obese*** *(n=144 cases)*					*P*-value for interaction: 0.43
Cases/person-years	45/161,481	65/290,699	34/245,613		
Crude HR (95% CI)	1.00	1.03 (0.67-1.57)	0.53 (0.28-1.03)	0.11	0.90 (0.77-1.05)
Multivariate HR (95% CI)	1.00	1.06 (0.69-1.64)	0.56 (0.29-1.08)	0.14	0.91 (0.78-1.08)
‡ ***Overweight*** *(n=363 cases)*					
Cases/person-years	115/478,180	164/ 837,232	84/527,638		
Crude HR (95% CI)	1.00	0.99 (0.77-1.28)	1.05 (0.72-1.53)	0.83	0.99 (0.90-1.09)
Multivariate HR (95% CI)	1.00	1.08 (0.83-1.40)	1.19 (0.81-1.73)	0.38	1.03 (0.94-1.14)
‡ ***Normal weight*** *(n=358 cases)*					
Cases/person-years	117/605,535	173/1,355,804	68/760,817		
Crude HR (95% CI)	1.00	0.90 (0.70-1.16)	0.92 (0.64-1.32)	0.56	0.98 (0.94-1.03)
Multivariate HR (95% CI)	1.00	0.97 (0.75-1.25)	1.02 (0.70-1.47)	0.97	1.00 (0.90-1.10)

Table 2: Hazard ratios (95% confidence intervals) of pancreatic cancer by country-specific levels of adherence to the arMED score in the EPIC cohort (n = 477,309). (continued)

	arMED Score				per 2 unit increment in arMED score
	Low (0-5) HR (95% CI)	Medium (6-9) HR (95% CI)	High (10-16) HR (95% CI)	*P-value* for trend	HR (95% CI)
Physically Active *(n=173 cases)*					*P*-value for interaction: 0.46
Cases/person-years	117/555,538	157/980,914	49/560,756		
Crude HR (95% CI)	1.00	1.04 (0.80-1.34)	0.81 (0.53-1.24)	0.53	0.98 (0.89-1.09)
Multivariate HR (95% CI)	1.00	1.09 (0.84-1.41)	0.89 (0.58-1.36)	0.86	1.01 (0.91-1.12)
Non-physically active *(n=505 cases)*					
Cases/person-years	151/596,061	220/1,231,169	134/908,833		
Crude HR (95% CI)	1.00	0.88 (0.70-1.10)	0.92 (0.67-1.26)	0.58	0.97 (0.89-1.05)
Multivariate HR (95% CI)	1.00	0.94 (0.75-1.18)	1.04 (0.75-1.43)	0.89	1.00 (0.92-1.09)
† ***Non-drinkers*** *(n=109 cases)*					*P*-value for interaction: 0.20
Cases/person-years	34/127,697	45/300,841	30/277,857		
Crude HR (95% CI)	1.00	0.78 (0.48-1.27)	0.68 (0.33-1.39)	0.26	0.92 (0.77-1.11)
Multivariate HR (95% CI)	1.00	0.84 (0.51-1.39)	0.78 (0.38-1.63)	0.49	0.97 (0.80-1.16)
† **Moderate drinkers** *(n=437 cases)*					
Cases/person-years	120/697,692	123/1,422,417	104/836,632		
Crude HR (95% CI)	1.00	1.08 (0.85-1.37)	1.13 (0.81-1.58)	0.46	1.03 (0.94-1.12)
Multivariate HR (95% CI)	1.00	1.12 (0.88-1.43)	1.20 (0.86-1.69)	0.27	1.05 (0.96-1.15)
† ***Drinkers*** *(n=319 cases)*					
Cases/person-years	123/419,807	144/760,477	52/419,578		
Crude HR (95% CI)	1.00	0.85 (0.66-1.11)	0.73 (0.48-1.11)	0.12	0.90 (0.81-1.00)
Multivariate HR (95% CI)	1.00	0.95 (0.73-1.24)	0.84 (0.55-1.29)	0.45	0.95 (0.85-1.05)
‡ ***Abdominal Obese*** *(n=237 cases)*					*P*-value for interaction: 0.76
Cases/person-years	69/226,129	106/373,247	62/328,889		
Crude HR (95% CI)	1.00	1.20 (0.87-1.67)	0.87 (0.53-1.44)	0.84	0.96 (0.85-1.09)
Multivariate HR (95% CI)	1.00	1.29 (0.92-1.80)	0.98 (0.59-1.62)	0.80	0.99 (0.87-1.12)
‡ ***Normal/moderate WC*** *(n=522 cases)*					
Cases/person-years	172/727,819	247/1,465,094	103/990,891		
Crude HR (95% CI)	1.00	0.90 (0.74-1.11)	0.82 (0.60-1.12)	0.20	0.97 (0.89-1.05)
Multivariate HR (95% CI)	1.00	0.97 (0.79-1.20)	0.94 (0.68-1.28)	0.68	1.01 (0.93-1.09)
* ***Southern Europe*** *(n=163 cases)*					*P*-value for interaction: 0.11
Cases/person-years	2/22,293	67/434,389	94/774,018		
Crude HR (95% CI)	1.00	1.57 (0.38-6.48)	1.07 (0.26-4.45)	0.06	0.86 (0.74-1.00)
Multivariate HR (95% CI)	1.00	1.60 (0.39-6.61)	1.16 (0.28-4.81)	0.12	0.88 (0.76-1.03)
* ***Central Europe*** *(n=341 cases)*					
Cases/person-years	93/577,960	179/1,255,044	69/616,619		
Crude HR (95% CI)	1.00	1.06 (0.82-1.38)	1.25 (0.87-1.80)	0.25	1.04 (0.94-1.15)
Multivariate HR (95% CI)	1.00	1.10 (0.85-1.44)	1.33 (0.92-1.93)	0.14	1.06 (0.96-1.17)
* ***Northern Europe*** *(n=361 cases)*					
Cases/person-years	182/644,942	156/794,302	23/143,430		
Crude HR (95% CI)	1.00	0.83 (0.67-1.04)	0.79 (0.50-1.23)	0.10	0.94 (0.85-1.03)
Multivariate HR (95% CI)	1.00	0.92 (0.73-1.15)	0.93 (0.59-1.47)	0.52	0.99 (0.90-1.09)

Crude HRs - stratified by age (1-year categories), sex, and centre.

Multivariate HRs - adjusted for total energy intake (continuous), body mass index (continuous), smoking status and intensity (never; current, 1-15 cigarettes per day; current, 16-25 cigarettes per day; current, 26+ cigarettes per day; former, quit ≤10 years; former, quit 11-20 years; former, quit 20+ years; current, pipe/cigar/occasional; current/former, missing; unknown), alcohol intake (non-drinkers, drinkers of 0-6 g/d, >6-12 g/d, >12-24g/d, >24-60 g/d, women drinkers of: >60g/d, men drinkers of: >60-96 g/d, >96 g/d), diabetes (verified, not verified but self-reported, not diabetes, missing), and stratified by age (1-year categories), sex, and centre.

†Non-drinkers: 0 drinks/d (0 g/d alcohol); moderate drinkers: no more than 1 drink/d (< 12g/d alcohol); ; drinkers: more than 1 drink/d (> 12 g/d alcohol).

‡ Obese, overweight and normal weight was defined according to WHO criteria, as ≥ 30 kg/m^2, 25 – 30 kg/m^2 and ≤ 25 kg/m^2, respectively.

Abdominal obesity, according to NCEP/ATPIII criteria, was defined as waist circumference ≥ 102 cm in men or ≥ 88 cm in women, and normal and moderate waist circumference as < 120 cm or < 88 cm in men and women, respectively. Multivariate HRs additionally controlling for BMI retrieved similar estimates.

*Southern Europe: Spain, Italy and Greece; Central Europe: France, Germany, UK and The Netherlands; Northern Europe: Sweden, Denmark and Norway

Table 3: Hazard ratios (HRs) and 95% confidence intervals (CIs) of pancreatic cancer associated with the arMED score in the EPIC cohort (n = 477,309) after removing score components one at a time.

arMED component (g/day)	Mean ± sd	HR* (95% CI)			*P-value* for trend	per 2 unit increment in arMED score HR (95% CI)
		Low (0-5) HR (95% CI)	Medium (6-9) HR (95% CI)	High (10-16) HR (95% CI)		
Vegetables†	106.7 ± 74.3	1.00	0.98 (0.84-1.15)	0.94 (0.71-1.26)	0.72	0.99 (0.92-1.06)
Fruits†	120.2 ± 90.5	1.00	1.03 (0.88-1.21)	1.02 (0.77-1.35)	0.79	1.00 (0.93-1.07)
Legumes†	7.1 ± 11.0	1.00	1.05 (0.90-1.23)	1.02 (0.78-1.34)	0.69	1.00 (0.94-1.07)
Fish†	18.9 ± 19.1	1.00	1.04 (0.88-1.23)	1.04 (0.78-1.37)	0.69	0.99 (0.96-1.03)
Cereals†	161.5 ± 110.8	1.00	0.98 (0.83-1.15)	0.89 (0.67-1.18)	0.50	1.00 (0.94-1.08)
Olive oil†	3.3 ± 6.7	1.00	0.91 (0.78-1.06)	1.00 (0.77-1.30)	0.62	0.99 (0.93-1.06)
Meat†	47.4 ± 25.0	1.00	1.02 (0.86-1.20)	1.08 (0.82-1.42)	0.64	1.00 (0.94-1.08)
Diary products†	161.5 ± 110.8	1.00	1.04 (0.88-1.23)	1.09 (0.83-1.44)	0.51	1.01 (0.94-1.08)
Alcohol‡	0.4 ± 0.5	1.00	1.01 (0.85-1.19)	0.99 (0.77-1.26)	0.95	1.00 (0.94-1.06)

*Multivariate HRs - adjusted for total energy intake (continuous), body mass index (continuous), smoking status and intensity (never; current , 1-15 cigarettes per day; current, 16-25 cigarettes per day; current, 26+ cigarettes per day; former, quit ≤10 years; former, quit 11-20 years; former, quit 20+ years; current, pipe/cigar/occasional; current/former, missing; unknown), alcohol intake (non-drinkers, drinkers of 0-6 g/d, >6-12 g/d, >12-24g/d, >24-60 g/d, women drinkers of: >60g/d, men drinkers of: >60-96 g/d, >96 g/d), diabetes (verified, not verified but self-reported, not diabetes, missing), and stratified by age (1-year categories), sex, and centre.

Intakes adjusted by energy intake (1,000 kcal)
† Referers to the arMED score. Adherence score is based on 14 points.
‡ Refers to the rMED score. Adherence score is based on 16 points
Multivariate HRs did not include alcohol intake.