



## Nutritional Epidemiology

## The Association of Diabetes-Related Dietary Patterns with Pancreatic Cancer Risk in the European Prospective Investigation into Cancer and Nutrition Study

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### A B S T R A C T

**Background:** Pancreatic cancer is relatively rare but remains one of the most lethal tumors. Identifying modifiable risk factors is a crucial step to reduce disease burden. Evidence suggests a potential role of type 2 diabetes mellitus in its pathogenesis.

**Objectives:** The objective of this study is to examine the association between dietary patterns related to diabetes and pancreatic cancer risk in a European population.

**Methods:** A total of 367,395 participants from the European Prospective Investigation into Cancer and Nutrition study were included. After a median follow-up of 14.9 y, 926 incident cases were identified. The Diabetes Risk Reduction Diet (DRRD), the Empirical Dietary Index for Hyperinsulinemia (EDIH), and the Empirical Dietary Index for Insulin Resistance (EDIR) were estimated from food frequency questionnaires at recruitment. Hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between dietary patterns and pancreatic cancer were calculated using multivariable Cox proportional hazards regression models, adjusted for relevant confounders.

**Results:** Adherence to DRRD showed no association with risk of pancreatic cancer (HR<sub>T3vsT1</sub>: 0.94; 95% CI: 0.79, 1.12). Higher adherence to EDIH was associated with a borderline 19% increased pancreatic cancer risk (HR<sub>T3vsT1</sub>: 1.19; 95% CI: 0.99, 1.44). No significant associations were observed in relation to EDIR. No heterogeneity was observed among the subgroups.

**Abbreviations:** CI, confidence interval; DRRD, Diabetes Risk Reduction Diet; EDIH, Empirical Dietary Index for Hyperinsulinemia; EDIR, Empirical Dietary Index for Insulin Resistance; EPIC, European Prospective Investigation into Cancer and Nutrition; FFQ, food frequency questionnaire; HR, hazard ratio; IGF-1, insulin-like growth factor-1; PC, pancreatic cancer; T2DM, type 2 diabetes mellitus; TG, triglyceride.

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**Conclusions:** Higher adherence to a hyperinsulinemic dietary pattern may contribute to risk of developing pancreatic cancer in our population. Further research is warranted to elucidate the potential role of dietary factors in cancer risk prevention.

**Keywords:** diabetes, dietary patterns, pancreatic cancer, etiology, risk

## Introduction

Pancreatic cancer (PC) is a complex and multifactorial disease whose early stages are often clinically silent and typically do not produce symptoms. As a result, the disease is frequently detected only when the tumor is advanced and has invaded surrounding tissues or organs [1], making early detection and treatment challenging. By the year 2022, an estimated 510,992 new cases of PC were reported worldwide, and 467,409 deaths were recorded [2]. Although it ranks as the 15th most commonly diagnosed cancer globally, its incidence has been increasing, particularly in North America and Europe [2].

The main risk factors include family history, chronic pancreatitis, older age, male sex, tobacco smoking, type 2 diabetes mellitus (T2DM), and excess body fatness [1,3]. According to the recent report from the World Cancer Research Fund and the American Institute for Cancer Research, each 5-unit increase in BMI (in kg/m<sup>2</sup>) is associated with an ~10% higher risk of PC, indicating a dose–response relationship [3]. Therefore, primary prevention focusing on modifiable risk factors may help reduce the incidence of PC.

Several food groups and nutrients, including red and processed meats, SFAs, total fat, and foods and beverages high in fructose, have been investigated for their potential association with PC risk [3,4]; however, evidence remains limited. Other studies suggest that higher consumption of nuts, reduced intake of fructose, red meat, and alcohol [5], and adherence to healthy dietary patterns may decrease risk, whereas Western-type diets and heavy drinking may increase it [6]. Despite these observations, overall evidence remains inconsistent. In this context, a dietary pattern approach may be particularly appropriate for investigating the association between diet and PC risk, as it is more comprehensive and considers the complex interactions among different dietary components [7]. Additionally, focusing on dietary patterns linked to specific mechanisms, such as T2DM, insulin resistance, and hyperinsulinemia, which are key underlying etiological mechanisms of PC, may provide additional insight beyond overall diet quality indices because these pathway-specific patterns are designed to capture metabolic processes that are implicated in the development of PC. For this reason, the aim of this study was to evaluate the association between dietary patterns related to these metabolic pathways and PC risk in a large prospective cohort.

## Methods

### Study population

The present analysis has been developed in the context of the European Prospective Investigation into Cancer and Nutrition (EPIC) study. This cohort is one of the largest ongoing prospective studies on diet, nutritional status, lifestyle, environmental factors, and incidence of cancer and other chronic diseases. The study design has been described previously [8].

Briefly, EPIC includes nearly half a million participants recruited between 1992 and 2000 from 10 European countries. Informed consent was obtained from all participants involved in the study during recruitment. The EPIC study was approved by the Ethics Committee of the International Agency for Research on Cancer in Lyon, France, as well as the local ethics committee of each study center. Data regarding diet, biological samples, lifestyle information, medical history, and anthropometric measurements were collected at recruitment. For this analysis, participants from Greece, Norway, and Sweden were excluded for administrative reasons, along with individuals with missing dietary data, those with neuroendocrine tumors, and participants diagnosed with PC in the first 2 y of follow-up, to avoid potential reverse causality. Details of the final study population are shown in [Supplemental Figure 1](#). In total, 367,395 participants were included for the analysis.

Cancer incidence information was assessed through population-based cancer registries in Denmark, Italy, the Netherlands, Norway, Spain, Sweden, and the United Kingdom, and through a combination of health insurance records, cancer and pathology registries, and active follow-up in France, Germany, and Greece [8]. The PC cases were classified as C25 (C25.0–C25.3 and C25.7–C25.9), based on the International Statistical Classification of Diseases and Related Health Problems. In a median follow-up of 14.9 y, 926 incident PC cases were identified among the participants.

### Dietary information

To collect dietary information, EPIC centers used 1 of 3 types of validated, country- and center-specific instruments: self-administered quantitative dietary questionnaires, semi-quantitative food frequency questionnaires (FFQs), and in some centers, combined dietary methods that included 7 to 14 d records or short nonquantitative FFQs [8]. To account for potential variability from different dietary assessment methods, an additional 24-h dietary recall was conducted in 5% to 12% of participants from each center [8]. To comprehensively evaluate dietary patterns related to T2DM, we calculated 3 diabetes-related dietary patterns for each participant: the Diabetes Risk Reduction Diet (DRRD) [9], the Empirical Dietary Index for Hyperinsulinemia (EDIH), and the Empirical Dietary Index for Insulin Resistance (EDIR) [10]. These patterns were selected because they capture key metabolic pathways such as hyperinsulinemia and insulin resistance, which may contribute to the development of PC [3], offering a mechanistic insight beyond general diet quality.

The DRRD used in this study is the version proposed by Kang et al. [9], which was developed with the objective of emphasizing the intake of multiple factors associated with a lower T2DM risk. The pattern includes the dietary glycemic index, the ratio of polyunsaturated to saturated fat, and the intake of trans fats, sugar-sweetened beverages and fruit juices, red and processed meats, cereal fiber, coffee, nuts, and whole fruits. For each participant, the consumption of these components was

standardized into quintiles based on the distribution across the entire study population. Each of the 9 components was then assigned a score from 1 to 5, and the sum of these values resulted in a total score ranging from 9 to 45. A higher score reflects better overall dietary quality. Therefore, the interpretation is that a higher DRRD score is inversely associated with T2DM risk.

The EDIH and EDIR are mechanistically based dietary patterns, developed by Tabung et al. [10], and are developed to predict hyperinsulinemia and insulin resistance, respectively, based on predicted concentrations of insulin-response biomarkers. Each pattern includes 18 food groups, although the specific groups differ between them. Food groups positively associated with the patterns include red and processed meats, low-energy beverages, soups, margarine, seafood other than dark-meat fish, and tomatoes, among others; whereas those inversely associated include wine, coffee, high-fat dairy products, green vegetables, and others. To calculate the scores, the intake of each food group was standardized by converting values into Z-scores by subtracting the mean and dividing by the SD. Each Z-score was then multiplied by its corresponding insulinemic potential weight, as described in the original publication [10]. Finally, all weighted values were summed to obtain each participant's final score. The EDIH and EDIR are dietary patterns that directly correlate with insulin-response biomarkers. EDIH uses C-peptide concentration to assess hyperinsulinemic potential, as this peptide is a useful marker of  $\beta$ -cell secretory function [11]. The resulting score ranges from lower to higher values, where higher scores indicate that the individual consumes a diet that may produce greater states of hyperinsulinemia. The EDIR uses the ratio of fasting triglycerides (TGs) to fasting HDL (TG/HDL) as a biomarker to assess insulin resistance. The TG/HDL ratio is associated with insulin resistance because elevated TG concentrations increase tissue exposure to free fatty acids, which can impair insulin sensitivity. In addition, oxidative stress and inflammation contribute to insulin resistance, and because HDL has antioxidant and anti-inflammatory properties, reduced HDL concentrations may indirectly promote insulin resistance [12]. Thus, higher EDIR values reflect a diet linked to an increased risk of insulin resistance.

All food groups used to calculate these patterns were standardized to 2000 kcal. For each of the 3 dietary patterns, values were truncated at  $\pm 3$  SDs to exclude potential outliers. This approach was used to minimize the impact of extreme values that could distort the analysis and lead to misleading conclusions. Details of the components of each dietary pattern according to consumption mean, SD, and tertiles of adherence in our study population are described in [Supplemental Table 1](#).

## Statistical analysis

The main characteristics of study participants were expressed as mean and SD for continuous variables and as frequencies and percentages for categorical variables. To assess the association between dietary patterns and PC risk, hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using Cox proportional hazards models. The Cox model applies a form of multiple linear regression to the logarithm of the incidence rate, with explanatory variables as predictors and the baseline incidence rate serving as a time-varying intercept [13]. In risk models, cohort entry time was defined as the age at recruitment, and exit time was defined as the age at PC diagnosis, death, end of follow-up, or last

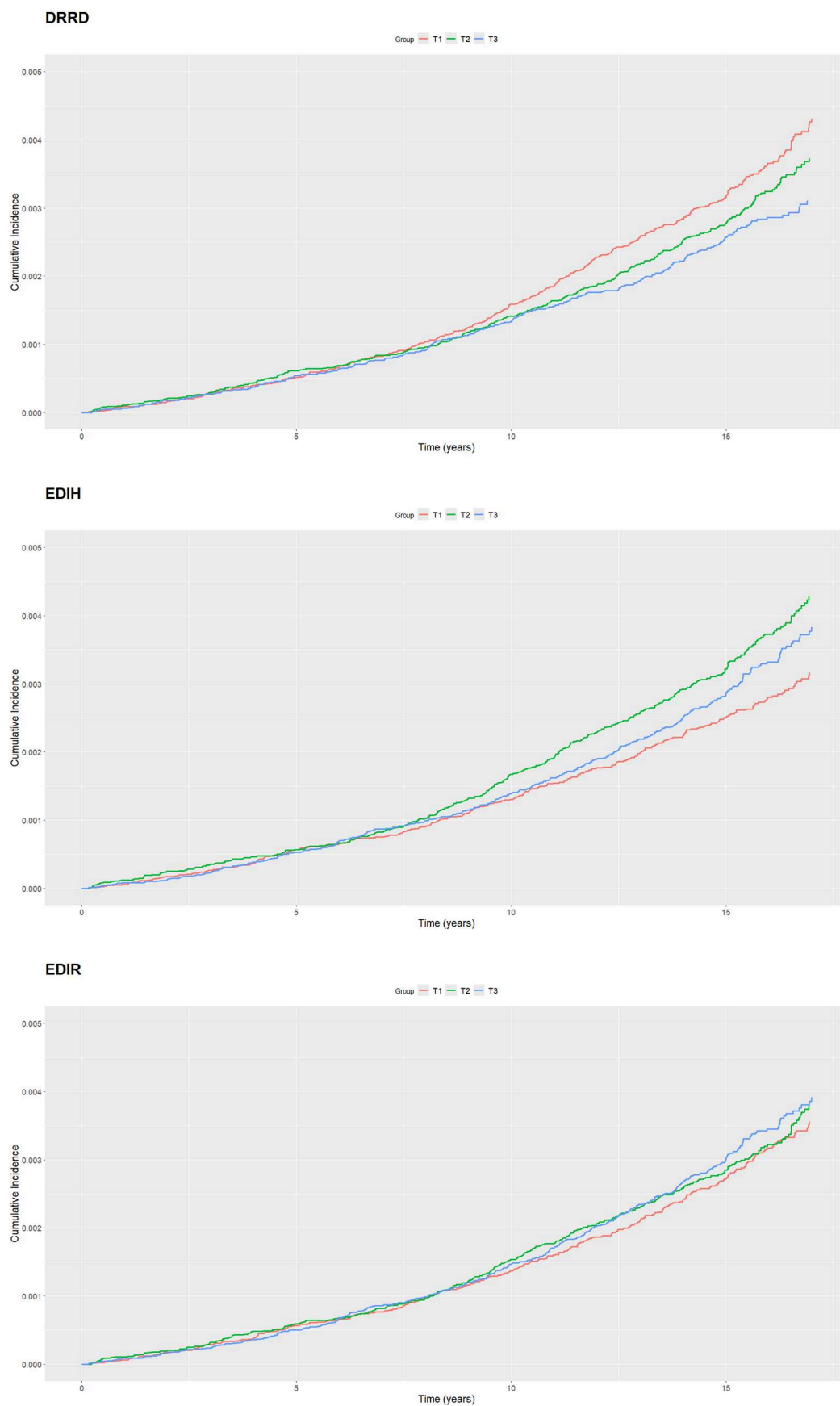
known contact, whichever occurred first. All models were stratified by country, sex, and age in 10-y categories. The variables included in the multivariable models were selected based on their reported association with PC risk in the literature and a sequential analyses of deviance based on likelihood ratio tests to identify

**TABLE 1**

Baseline characteristics of the 367,395 participants and the 926 PC cases in the European Prospective Investigation into Cancer and Nutrition population

| Variable                                        | Participants<br>(N = 367,395) | %    | PC cases<br>(N = 926) | %    |
|-------------------------------------------------|-------------------------------|------|-----------------------|------|
| <b>Dietary patterns</b>                         |                               |      |                       |      |
| Mean (SD)                                       |                               |      |                       |      |
| DRRD                                            | 27 (4.2)                      |      | 26 (4.4)              |      |
| EDIH                                            | −0.05 (0.8)                   |      | −0.06 (0.7)           |      |
| EDIR                                            | −0.01 (0.7)                   |      | −0.01 (0.7)           |      |
| <b>Sex</b>                                      |                               |      |                       |      |
| Female                                          | 258,313                       | 70.3 | 524                   | 56.6 |
| Male                                            | 109,082                       | 29.7 | 402                   | 43.4 |
| <b>Country</b>                                  |                               |      |                       |      |
| Denmark                                         | 54,996                        | 15.0 | 307                   | 33.2 |
| France                                          | 67,399                        | 18.3 | 52                    | 5.6  |
| Germany                                         | 48,540                        | 13.2 | 99                    | 10.7 |
| Italy                                           | 44,536                        | 12.1 | 95                    | 10.3 |
| Spain                                           | 39,984                        | 10.9 | 103                   | 11.1 |
| The Netherlands                                 | 36,533                        | 9.9  | 90                    | 9.7  |
| United Kingdom                                  | 75,407                        | 20.5 | 180                   | 19.4 |
| <b>Age at recruitment (y)</b>                   |                               |      |                       |      |
| Mean (SD)                                       | 51.3 (9.9)                    |      | 57.6 (7.4)            |      |
| <50                                             | 150,442                       | 40.9 | 112                   | 12.1 |
| 50 to <60                                       | 146,393                       | 39.9 | 471                   | 50.9 |
| ≥60                                             | 70,560                        | 19.2 | 343                   | 37.0 |
| <b>Educational level</b>                        |                               |      |                       |      |
| None                                            | 14,872                        | 4.1  | 47                    | 5.1  |
| Primary                                         | 86,978                        | 23.7 | 307                   | 33.2 |
| Secondary                                       | 75,011                        | 20.4 | 127                   | 13.7 |
| Technical                                       | 80,009                        | 21.8 | 214                   | 23.1 |
| Longer (university)                             | 93,871                        | 25.6 | 178                   | 19.2 |
| Unknown                                         | 16,654                        | 4.5  | 53                    | 5.7  |
| <b>BMI (kg/m<sup>2</sup>)</b>                   |                               |      |                       |      |
| Mean (SD)                                       | 25.4 (4.2)                    |      | 26.5 (4.3)            |      |
| <18.5                                           | 5952                          | 1.6  | 4                     | 0.4  |
| 18.5 to <25                                     | 185,986                       | 50.6 | 377                   | 40.7 |
| 25 to <30                                       | 127,620                       | 34.7 | 376                   | 40.6 |
| >30                                             | 47,837                        | 13.0 | 169                   | 18.3 |
| <b>Alcohol consumption (g/d)</b>                |                               |      |                       |      |
| Mean (SD)                                       | 13.2 (17.9)                   |      | 17.5 (22.2)           |      |
| <5                                              | 158,447                       | 43.1 | 352                   | 38.0 |
| 5 to 15                                         | 102,205                       | 27.8 | 226                   | 24.4 |
| >15                                             | 106,743                       | 29.1 | 348                   | 37.6 |
| <b>Smoking intensity</b>                        |                               |      |                       |      |
| Never                                           | 159,107                       | 43.3 | 346                   | 37.4 |
| Former                                          | 95,573                        | 26.0 | 250                   | 27.0 |
| Smoker                                          | 102,116                       | 27.8 | 303                   | 32.7 |
| Unknown                                         | 10,599                        | 2.9  | 27                    | 2.9  |
| <b>Cambridge physical activity index</b>        |                               |      |                       |      |
| Inactive                                        | 76,522                        | 20.8 | 222                   | 24.0 |
| Moderately inactive                             | 125,339                       | 34.1 | 303                   | 32.7 |
| Moderately active                               | 88,110                        | 24.0 | 188                   | 20.3 |
| Active                                          | 70,682                        | 19.2 | 196                   | 21.2 |
| Unknown                                         | 6742                          | 1.8  | 17                    | 1.8  |
| <b>Diabetes mellitus type 2 (self-reported)</b> |                               |      |                       |      |
| Yes                                             | 9286                          | 2.5  | 47                    | 5.1  |
| No                                              | 328,205                       | 89.3 | 777                   | 83.9 |
| Unknown                                         | 29,904                        | 8.1  | 102                   | 11.0 |

Abbreviations: DRRD, Diabetes Risk Reduction Diet; EDIH, Empirical Dietary Index for Hyperinsulinemia; EDIR, Empirical Dietary Index for Insulin Resistance; PC, pancreatic cancer.



**FIGURE 1.** Cumulative incidence (unadjusted) of PC during the follow-up period according to DRRD, EDIH, and EDIR. DRRD, Diabetes Risk Reduction Diet; EDIH, Empirical Dietary Index for Hyperinsulinemia; EDIR, Empirical Dietary Index for Insulin Resistance; PC, pancreatic cancer.

covariates that significantly contributed to the models. Model 1 was adjusted for energy intake (kilocalories per day) (continuous), alcohol intake (<5 g; 5–15 g; >15 g/d), BMI (continuous), and a smoking variable combining smoking status and intensity (never smokers; former smokers categorized by time since smoking cessation in ≤10, 11–20, and >20 y; current smokers categorized by the number of cigarettes smoked per day from 1–10, 11–20, 21–25, ≥26 cigarettes/d; and unknown smoking status). Model 2 was further adjusted for self-reported T2DM (no; yes; unknown). Subgroup analyses were performed by age (<50; 50–60; >60 y at recruitment), sex (women; men), BMI (<25; ≥25), alcohol consumption (nonconsumers <5 g; 5–15 g; >15 g/d), and smoking status (never; former; smoker). Comparison between subgroups with and without T2DM was not possible because of the small number of PC cases with self-reported diabetes (*n* = 47). Additionally, we conducted 3 sensitivity analyses to evaluate the robustness of the results, one excluding participants who self-reported a diagnosis of T2DM to assess whether the potential association between dietary intake and cancer risk was independent of pre-existing diabetes. Second, the models without adjustment for BMI, given that adiposity may lie on the causal pathway between diet and PC risk. Finally, we fitted models including each of the 44 individual food components of the dietary patterns as independent variables to examine whether specific dietary components were driving the observed associations.

The analysis excluded participants diagnosed within the first 2 y of follow-up to minimize potential reverse causality arising from changes in diet or lifestyle due to pre-existing subclinical conditions. This exclusion period was selected based on evidence from previous studies [14]. The derivation of the final study sample, including the numbers of participants excluded at each step, is shown in Supplemental Figure 1. The dietary patterns were evaluated using restricted cubic splines to assess potential nonlinear associations. Because EDIH did not fit a linear model, categorical analyses using tertiles provided the most appropriate representation of its nonlinear relationship with the outcome of PC. In contrast, DRRD and EDIR showed

approximately linear associations; however, they were also categorized into tertiles to allow comparability across dietary patterns and interpretation of the results. The spline curves supporting these models are presented in Supplemental Figure 2. For the categorical analysis, the first tertile was used as the reference category. Tests for linear trend across tertiles were performed by modeling the ordinal tertile variable as a continuous term. The tertile distribution in the DRRD is not uniform across the 3 groups, as a substantial number of participants have values that fall at the cutoff of the tertiles. To assess whether the association between adherence to the dietary patterns and PC risk differed between subgroups, we used a likelihood ratio test comparing a base model with a model that included an interaction term. All statistical analyses were performed using RStudio version 4.4.3, and a *P* value of <0.05 was considered statistically significant.

Results

This analysis included a sample of 367,395 participants, of whom 926 developed PC during 14.9 y of prospective follow-up after exclusions. General characteristics of study participants and overall PC cases at baseline are presented in Table 1. Briefly, participants had a mean age of 51.3 y (SD 9.9), a mean BMI in the overweight range (25.4, SD 4.2), were more likely to be non-smokers, and tended to be moderately inactive. In contrast to the whole cohort, PC cases were older at recruitment (mean age 57.6 y, SD 7.4), were also overweight but with a higher mean BMI (26.5, SD 4.3), consumed more alcohol, smoked more, and were also moderately inactive. The dietary patterns had similar mean values in both the overall cohort and the PC cases. The correlation between the different dietary pattern scores was tested using Pearson correlation coefficients: DRRD and EDIH (−0.21), DRRD and EDIR (−0.28), EDIR and EDIH (0.87). Participant characteristics across tertiles of adherence to the different dietary patterns are shown in Supplemental Table 2. In summary, as participants showed greater adherence to the DRRD pattern, they consumed

TABLE 2  
Multivariable HR and 95% CI of adherence to DRRD, EDIR, EDIH, and PC risk

| Dietary pattern | Model             | Tertile 1        | Tertile 2         | Tertile 3         | P-trend |
|-----------------|-------------------|------------------|-------------------|-------------------|---------|
|                 |                   | HR (95% CI)      | HR (95% CI)       | HR (95% CI)       |         |
| DRRD            | <i>n</i> (events) | 132,550 (374)    | 134,140 (328)     | 100,705 (224)     |         |
|                 | Model 1           | 1.00 (reference) | 0.98 (0.85, 1.15) | 0.91 (0.77, 1.08) | 0.31    |
|                 | Model 2           | 1.00 (reference) | 1.02 (0.87, 1.18) | 0.96 (0.81, 1.14) | 0.71    |
|                 | Model 3           | 1.00 (reference) | 1.01 (0.86, 1.17) | 0.94 (0.79, 1.12) | 0.54    |
| EDIH            | <i>n</i> (events) | 122,465 (269)    | 122,465 (344)     | 122,465 (313)     |         |
|                 | Model 1           | 1.00 (reference) | 1.13 (0.96, 1.33) | 1.21 (1.01, 1.43) | 0.03    |
|                 | Model 2           | 1.00 (reference) | 1.13 (0.95, 1.33) | 1.19 (0.99, 1.44) | 0.06    |
|                 | Model 3           | 1.00 (reference) | 1.13 (0.96, 1.33) | 1.19 (0.99, 1.44) | 0.06    |
| EDIR            | <i>n</i> (events) | 122,465 (297)    | 122,465 (308)     | 122,465 (321)     |         |
|                 | Model 1           | 1.00 (reference) | 0.94 (0.80, 1.11) | 1.03 (0.88, 1.22) | 0.68    |
|                 | Model 2           | 1.00 (reference) | 0.96 (0.81, 1.13) | 1.05 (0.88, 1.26) | 0.58    |
|                 | Model 3           | 1.00 (reference) | 0.96 (0.81, 1.13) | 1.05 (0.88, 1.26) | 0.60    |

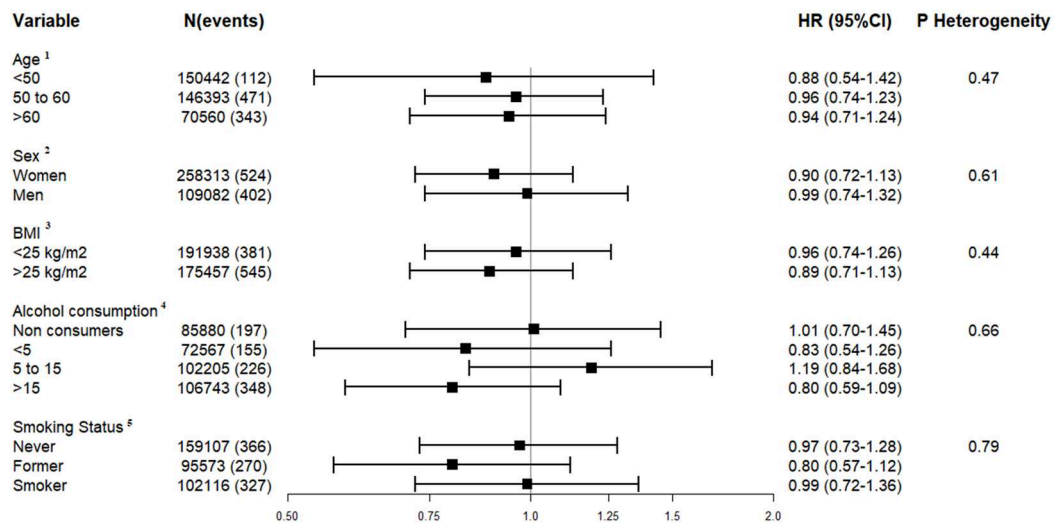
Abbreviations: CI, confidence intervals, DRRD, Diabetes Risk Reduction Diet; EDIH, Empirical Dietary Index for Hyperinsulinemia; EDIR, Empirical Dietary Index for Insulin Resistance; HR, hazard ratio.

Model 1: stratified by country, age, and sex.

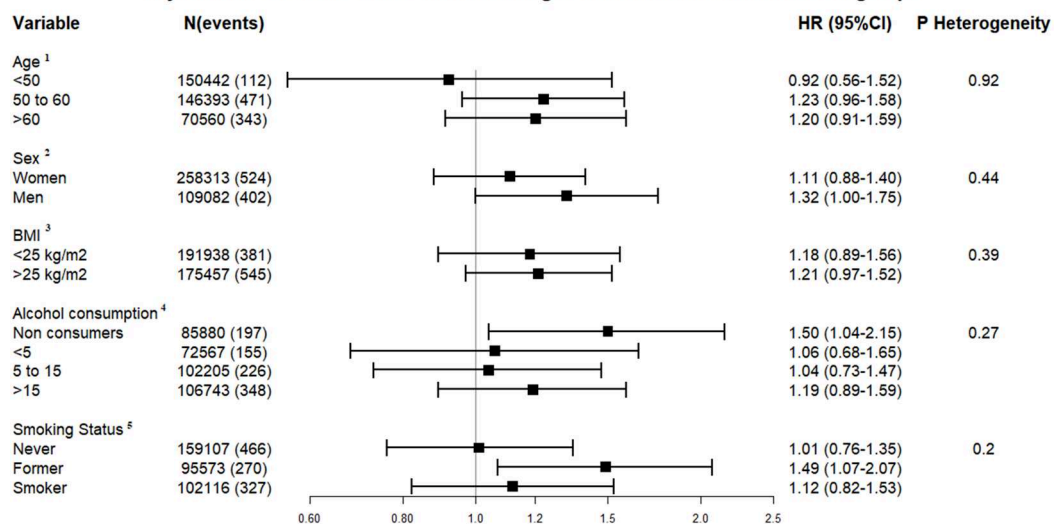
Model 2: model 1 further adjusted by energy kcal/d (continuous), alcohol intake (<5 g, 5–15 g, >15 g), BMI (continuous), and smoking status (never smokers; former smokers by time since smoking cessation ≤10, 11–20, >20 y since quitting; current smokers 1–10, 11–20, 21–25, ≥26 cigarettes/d; unknown status).

Model 3: model 2 further adjusted by self-reported diabetes mellitus (yes, no, and NA).

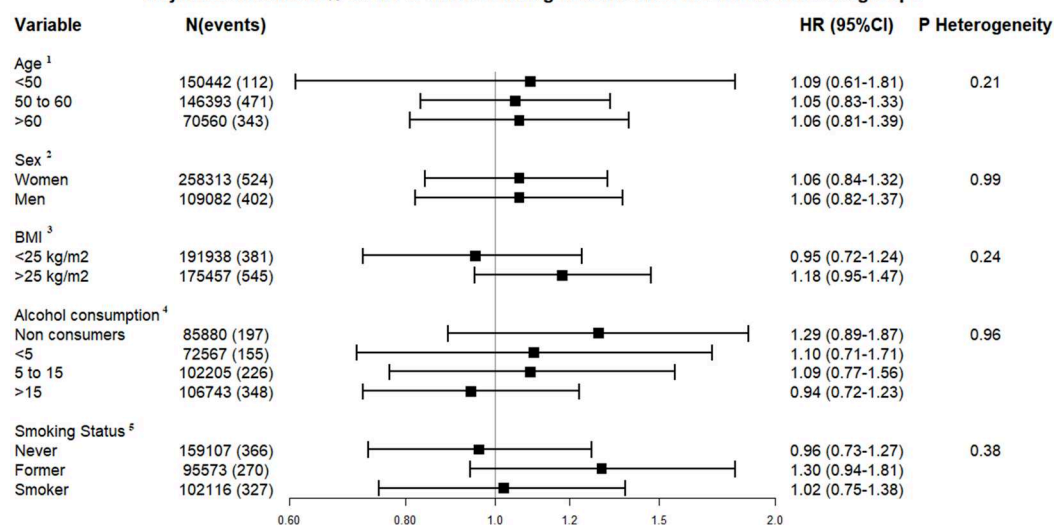
## Adjusted HR and 95% CI of PC risk according to adherence to DRRD across subgroups



## Adjusted HR and 95% CI of PC risk according to adherence to EDIH across subgroups



## Adjusted HR and 95% CI of PC risk according to adherence to EDIR across subgroups



(caption on next page)

fewer calories, had a higher educational level, and consumed less alcohol. No significant differences were observed between adherence to this pattern and BMI or physical activity. In contrast, participants with higher adherence to the EDIH and EDIR patterns had higher calorie intake, were more likely to be current smokers, and showed a slight tendency toward increased BMI across tertiles.

Figure 1 shows the unadjusted cumulative incidence of PC over time according to tertiles of adherence to each dietary pattern. For the healthier pattern, the DRRD, participants in the lowest tertile of adherence tended to show a higher incidence over time. In contrast, for the hyperinsulinemic pattern, the EDIH, higher incidence of PC was observed in the medium and higher levels of adherence. No clear differences were observed for EDIR. Table 2 shows the association between tertiles of adherence to each dietary pattern and PC risk. For the DRRD, no association was found in the fully adjusted model ( $HR_{T3vsT1}$ : 0.94; 95% CI: 0.79, 1.12;  $P$ -trend = 0.54). In relation to EDIH, a 19% borderline higher risk of PC was observed in the highest tertile of adherence than in the lowest tertile of adherence, after adjusting for multiple confounders ( $HR_{T3vsT1}$ : 1.19; 95% CI: 0.99, 1.44;  $P$ -trend = 0.06). Finally, no associations were observed for EDIR ( $HR_{T3vsT1}$ : 1.05; 95% CI: 0.88, 1.26;  $P$ -trend = 0.60). Sensitivity analyses excluding participants with self-reported T2DM and without adjustment for BMI yielded similar results, improving the statistical association between EDIH and PC risk (Supplemental Tables 3 and 4). As shown in Supplemental Table 5, most dietary components were not significantly associated with PC risk. Red meat was the only component consistently associated with a higher risk ( $HR_{T3vsT1}$ : 1.27; 95% CI: 1.04, 1.54), whereas fruit juice intake was inversely associated with risk ( $HR_{T3vsT1}$ : 0.81, 95% CI: 0.68, 0.96). The associations between adherence to dietary patterns and PC risk across subgroups of age, sex, BMI, alcohol consumption, and smoking status are shown in Figure 2. No statistically significant heterogeneity was detected across any of the subgroups examined.

## Discussion

In a large population of middle-aged European participants, including 926 PC cases, we found that higher adherence to a dietary pattern associated with hyperinsulinemia was associated with a borderline increased risk of PC. No significant results were found for the diabetes preventive pattern or a pattern related to insulin resistance. No differences across subgroups of age, sex, BMI, alcohol consumption, or smoking status were observed. Results remained unchanged after a sensitivity analysis excluding participants with self-reported T2DM. Furthermore, analyses of the individual dietary components suggested that the observed association was unlikely to be driven by any single food but rather reflected the combined effects of the

overall dietary patterns. Overall, our findings suggest that insulin-related pathways may be potentially implicated in PC, consistent with evidence that diabetes is a risk factor for the disease.

To the best of our knowledge, the association between the diabetes-related dietary patterns and PC risk has been assessed in 3 studies, 1 case-control study and 2 cohort studies. In the case-control study, which included 326 PC cases and 652 controls, the authors reported a 45% reduced risk of PC among participants with higher adherence to the DRRD ( $OR_{T3vsT1}$ : 0.55; 95% CI: 0.38, 0.80;  $P$ -trend = 0.002), even after excluding participants with a self-reported history of T2DM [15]. Although these results are promising, we acknowledge that comparisons between case-control and cohort studies may be inaccurate, as dietary differences could reflect consequences rather than causes of cancer. In addition, case-control designs are inherently more susceptible to selection and recall bias than cohort studies [5,6].

In the prostate, lung, colorectal, and ovarian cancer screening trial, a cohort with 402 incident PC cases, participants who were more adherent to the DRRD had a lower risk of PC ( $HR_{Q4vsQ1}$ : 0.62; 95% CI: 0.44, 0.86;  $P$ -trend = 0.004) [16]. Discrepancy between these results and ours may be explained by several factors, including differences in the version of the DRRD used. The study [16] applied the first version of DRRD, composed of 8 components [17], whereas our analysis used the recent version, which includes 9 components and distinguishes whole fruits as a protective factor from fruit juices as a risk factor for T2DM [9]. Additionally, differences in adherence to the DRRD may have contributed to the observed results. Our cohort reported higher adherence (range 14–39) than theirs (range 8–32), causing most of our participants to cluster near the top of the scale, reducing variability. This compression may diminish the contrast between the first and third tertiles, attenuating the associations.

Results from 850 PC cases in the Women's Health Initiative indicate an overall null association between EDIH and PC risk ( $HR_{Q5vsQ1}$ : 0.95; 95% CI: 0.75, 1.19). However, among women with longstanding T2DM, each 1-SD increase in EDIH was associated with a 33% higher risk of developing PC ( $HR$ : 1.33; 95% CI: 1.06, 1.66) [18]. Comparisons with our study are not straightforward, as the Women's Health Initiative included only women, whereas our cohort included both sexes. In our sex-stratified analyses, no association was observed between EDIH and PC risk among women ( $HR_{T3vsT1}$ : 1.11; 95% CI: 0.88, 1.40), while a positive association was initially suggested among men ( $HR_{T3vsT1}$ : 1.32; 95% CI: 1.00, 1.75); however, tests for heterogeneity by sex were not statistically significant ( $P$  for heterogeneity = 0.44), indicating no clear evidence of effect modification by sex. Although men have a higher overall risk of

**FIGURE 2.** Adjusted HR and 95% CI of PC risk according to DRRD, EDIR, and EDIH by subgroups of age, sex, BMI, alcohol consumption, and smoking status. CI, confidence interval; DRRD, Diabetes Risk Reduction Diet; EDIH, Empirical Dietary Index for Hyperinsulinemia; EDIR, Empirical Dietary Index for Insulin Resistance; HR, hazard ratio; PC, pancreatic cancer.

<sup>1</sup>Model: stratified by country and sex. Adjusted by alcohol intake (<5 g, 5–15 g, >15 g), BMI (continuous), smoking status and intensity (never, former smokers who quit ≤10 to >20 y ago, current smokers consuming 1 to ≥26 cigarettes/d, unknown), and self-reported diabetes mellitus (yes, no, and NA).

<sup>2</sup>Model: stratified by country and age. Adjusted by alcohol intake, BMI, smoking status and intensity, and self-reported diabetes mellitus.

<sup>3</sup>Model: stratified by country, age, and sex. Adjusted by alcohol intake, smoking status and intensity, and self-reported diabetes mellitus.

<sup>4</sup>Model: stratified by country, age, and sex. Adjusted by BMI, smoking status and intensity, and self-reported diabetes mellitus.

<sup>5</sup>Model: stratified by country, age, and sex. Adjusted by alcohol intake, BMI, and self-reported diabetes mellitus.

PC than women, this difference does not appear to modify the association between EDIH and PC risk in our data. Nevertheless, the inclusion of only women in the cited study [18] may have limited its ability to detect associations observed in more heterogeneous populations like ours, and thus represents a potential limitation of that analysis. Nonetheless, both our overall results and the findings from the longstanding T2DM subgroup of the Women's Health Initiative support the hypothesis that T2DM may contribute to pancreatic carcinogenesis, potentially through chronic hyperinsulinemia and progressive  $\beta$ -cell dysfunction, ultimately increasing the likelihood of developing PC [19,20].

The relationship between other diabetogenic dietary factors has been evaluated in previous studies using different approaches, such as the glycemic index, which is one of the components of the DRRD. In the Women's Health Initiative observational study [21], researchers found no association between the dietary glycemic index and PC risk ( $HR_{Q4vsQ1}$ : 1.13; 95% CI: 0.78, 1.63;  $P$ -trend = 0.94), consistent with the limited not conclusive evidence in the last report from the World Cancer Research Fund and the American Institute for Cancer Research [3]. Because the contribution of hyperinsulinemia vs. hyperglycemia to PC risk remains uncertain, the use of an insulin index instead of a glycemic index has been proposed. A study based on this hypothesis was conducted within the Nurses' Health Study and the Health Professionals Follow-Up Study [22]. However, in contrast with our EDIH results, no overall associations were observed, and significant findings were only noted among overweight and inactive participants.

In our results, EDIR showed no associations with PC risk, in contrast to EDIH. This suggests that, in our population, EDIH may be a more effective dietary pattern for capturing associations between chronic hyperinsulinemia and PC. EDIH was originally developed using fasting plasma C-peptide concentrations, a biomarker that is influenced by acute dietary intake and that may as well reflect insulin resistance states characterized by sustained elevated insulin concentrations [11]. Therefore, EDIH may more accurately capture the chronic insulinemic environment, which is also closely associated with reduced insulin sensitivity. Furthermore, evidence from a study analyzing 24-h urinary C-peptide concentrations has confirmed that EDIH is positively correlated with total daily insulin secretion [23], supporting its validity as an indicator of the overall insulinemic potential of the diet. Although EDIH and EDIR were highly correlated (Pearson correlation = 0.87), they are not interchangeable. Despite sharing several components such as red and processed meats, low-energy beverages, soups, margarine, seafood other than dark-meat fish, and tomatoes, they differ in the weighting and inclusion of specific food groups, which may lead to distinct associations with PC risk. In our study, EDIH included several foods associated with postprandial insulin secretion, such as high-energy beverages [24] that are not included in EDIR. In contrast, EDIR incorporated a broader range of vegetables and nuts, reflecting a more heterogeneous dietary pattern that includes multiple protective components. These additional components in EDIR could attenuate the overall association with PC risk. In conclusion, because of its broader scope, EDIH may have a greater ability to capture relevant diet-disease associations, not only with PC, as observed in our results, but also with

other cancers such as colorectal [25,26] and prostate cancer [27].

We aimed to assess the association between diabetes-related dietary patterns and PC risk, given the close and complex relationship between T2DM and PC. Although T2DM is a risk factor for PC, it may also arise as a consequence of tumor development [28], suggesting a bidirectional relationship. The biological mechanisms linking prolonged hyperinsulinemia and insulin resistance to pancreatic oncogenesis may involve a gradual and progressive deterioration of  $\beta$ -cell function [19]. This dysfunction, combined with a chronic proinflammatory state, may ultimately increase risk of developing PC. Hyperinsulinemia may influence circulating insulin-like growth factor-1 (IGF-1) concentrations, which has been proposed to contribute to tumor development through activation of mitogenic signaling pathways, including the phosphatidylinositol 3-kinase cascade [4]. However, the evidence linking IGF-1 specifically to PC remains limited [29]. This pathway regulates multiple cellular processes, including protein synthesis, cellular proliferation and differentiation, inhibition of apoptosis, and angiogenesis [18,20], thereby potentially supporting the development of precursor pancreatic lesions. The pancreas expresses IGF-1 receptors and may therefore be responsive to this signaling axis [4]. In parallel, elevated adipose tissue, especially in the mesenteric peri-pancreatic area, releases free fatty acids, hormones, and proteins that promote proinflammatory signaling and insulin resistance. Adipose tissue macrophages also produce TNF- $\alpha$  and ILs, further amplifying inflammatory pathways [19]. TNF- $\alpha$  receptors such as rTNF-R1 have been associated with an increased risk of PC in women, whereas rTNF-R2 may act as a mediator between the associations of overweight, diabetes, and PC within the EPIC cohort [30]. Thus, T2DM may promote PC through various mechanisms, such as altered signaling and metabolism and increased local inflammation.

The limitations of this study include that the FFQs were administered only at recruitment, and the median time between enrollment and diagnosis was 9.6 y. Without follow-up FFQs, we were unable to account for potential changes in diet over time. However, the dietary information collected is expected to reflect the etiologically relevant time window, which occurs before the onset of the disease, minimizing potential errors from including data corresponding to the cancer latency period. Different dietary assessment methods, including self-reported questionnaires, were used across EPIC centers. This may have led to recall errors or participants' lack of familiarity with the FFQs. To address this, EPIC collected additional dietary intake data using computer-assisted 24-h dietary recalls in a representative subsample. Furthermore, the FFQs used in the study have been previously validated and shown to have good reproducibility. We evaluated a limited set of 3 dietary patterns, and other indices could also be relevant. Our selection focused on patterns with mechanisms related to the outcome and supported by evidence linking them to insulin-related metabolic pathways, but other patterns might also capture additional aspects of the relationship between diet and PC. The dietary indices examined were developed based on food groups commonly consumed in Western populations; the generalizability of our findings to populations with substantially different dietary patterns may be limited. Given the observational nature of our study, residual

confounding cannot be excluded. Nonetheless, we adjusted for major confounders based on current evidence.

One of the major strengths of our study is the large sample size, drawn from multiple countries, along with the long follow-up period with detailed participant information. Another strength is the multifactorial analysis of key indicators related to PC, such as alcohol intake, BMI, and T2DM. Moreover, we examined standardized dietary patterns linked to biological mechanisms involved in PC etiology, including hyperinsulinemia assessed through C-peptide concentrations, insulin resistance indicated by the TG/HDL ratio, and broader dietary pattern related to diabetes prevention. These indices were previously developed and validated in independent prospective cohorts. Additionally, the food groups used to derive these dietary patterns are commonly consumed in Western populations, including European populations, making these indices particularly relevant for capturing the habitual dietary behavior of our study population. Consequently, the analysis of dietary patterns allows for a more comprehensive and integrative assessment of dietary characteristics and their synergistic effects.

Our results suggest that higher adherence to a dietary pattern that may increase states of hyperinsulinemia may be associated with risk of developing PC in a large European population. This may be due to the close relationship between T2DM and PC and the underlying mechanisms through which hyperinsulinemia and insulin resistance are related to unhealthy eating habits. Future studies are needed to confirm these associations in other populations, as prevention strategies based on lifestyle modification represent a promising approach to reduce PC burden.

## Disclaimer

Where authors are identified as personnel of the International Agency for Research on Cancer/World Health Organization, the authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policy or views of the International Agency for Research on Cancer/World Health Organization.

## Author contributions

The authors' responsibilities were as follows – MC-B: designed research; LT-L, WB: conducted research and analyzed data; LT-L, MC-B, AG, DA, FJ, LP-N, MBS, RTF, TT, VK: wrote the paper; RZ, CS, CC, LB, MTG, MJ, NCC, RT, SP: validated and reviewed the paper; MC-B, LT-L: primary responsible for final content; and all authors: read and approved the final manuscript.

## Conflict of interest

The authors report no conflicts of interest.

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## Data availability

Data described in the manuscript, code book, and analytic code will be made available upon request pending. The data presented in this study are preserved by the EPIC centers. Data are available for investigators who seek to answer important questions on health and disease in the context of research projects that are consistent with the legal and ethical standard practices of IARC/WHO and the EPIC centers. The primary responsibility for accessing the data belongs to IARC and the EPIC centers. Access to materials from the EPIC study can be requested by contacting [epic@iarc.fr](mailto:epic@iarc.fr).

## Declaration of Generative AI and AI-assisted technologies in the writing process

The authors declare that no generative AI or AI-assisted technologies were used in the writing of this manuscript.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.tjnnt.2026.101755>.

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