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Original Research

Major dietary patterns in the United Kingdom Women's Cohort Study showed no evidence of prospective association with pancreatic cancer risk

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ABSTRACT

Diet is a modifiable risk factor for pancreatic cancer. We hypothesized that specific dietary patterns would increase/decrease pancreatic cancer risk. We evaluated the association of dietary patterns with pancreatic cancer risk in the UK Women's Cohort Study. Dietary patterns were assessed at enrollment using: (1) self-reported practice of vegan/vegetarian dietary habits, (2) diet quality indices (World Health Organization Healthy Diet Indicator and Mediterranean Diet Score), and (3) principal component analysis-derived dietary patterns. The association of dietary patterns with pancreatic cancer incidence was quantified using Cox regression survival analysis. Over a median follow-up of 19 years of 35,365 respondents, there were 136 incident cases of pancreatic cancer. No association between dietary

Abbreviations: BMI, body mass index; CI, confidence interval; FFQ, food frequency questionnaire; IMU, International Medical University; MDS, Mediterranean diet score; PCA, principal component analysis; SD, standard deviation; UKWCS, United Kingdom Women's Cohort Study; WHO-PDI, World Health Organization-Healthy Diet Indicator.

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habits/quality and pancreatic cancer incidence was evident after adjustments (hazard ratio (95% confidence interval): self-reported omnivores vs vegan/vegetarian dietary habit: 1.13 (0.73-1.76); per-unit increase in World Health Organization Healthy Diet Indicator scores: 0.99 (0.91-1.09); per-unit increase in Mediterranean Diet Score: 0.92 (0.83-1.02). Similarly, no association of principal component analysis-derived dietary patterns with pancreatic cancer risk was evident ("prudent:" 1.02 [0.94-1.10]; "meat-based:'' 1.00 [0.92-1.09]; "fast-food, sugar-sweetened beverages, and carbohydrate-rich snacks:'' 0.96 [0.86-1.07]; "cereal and dairy-rich:'' 1.04 [0.94-1.16], and "low-diversity and lowfat:'' 1.00 [0.89-1.13]). In this prospective cohort of women, several major dietary patterns were of poor quality. There was no evidence of a prospective association between any of the dietary patterns explored and pancreatic cancer incidence.

1. Introduction

Pancreatic cancer has the highest mortality among cancers, with reported 5-year survival rates ranging between 2% and 9% [1–3]. However, modifiable risk factors such as cigarette smoking, physical inactivity, obesity, and diabetes mellitus account for approximately 90% of pancreatic cancer cases [3–6]. The implication of obesity and diabetes in the etiology of pancreatic cancer supports the attribution of up to 50% of pancreatic cancers to unhealthy diets [5]. Hence, understanding the influence of diet as a modifiable risk factor for pancreatic cancer is important.

Excessive intakes of energy, carbohydrate, fat, and high intakes of meat and red meat have individually been associated with an increased risk of pancreatic cancer in some studies [5]. In others, adequate fruit and vegetable intakes were associated with lowered pancreatic cancer risks [4]. However, the reductionist approach to studying single foods or nutrients is problematic because of the multidimensional nature of the diet and its relationship with diseases and could in part explain the equivocal nature of such evidence [5]. Foods are eaten in combination and contain several nutrients that interact with each other [7]. This interaction influences their bioavailability and absorption and; an excess of 1 food or nutrient may substitute for another [5,7]. To accommodate these complexities, nutritional epidemiology increasingly evaluates complete dietary patterns and their relationships with diseases [5,7,8]. Dietary pattern analysis evaluates quantity, variety, and the combination of different foods and beverages habitual diets include and account for interrelations of food choices [7,8]. Hence, studying dietary patterns complements the traditional approach to evaluate the association of food groups and nutrient intakes with the disease risk and may be particularly suitable when many dietary components are relevant for a disease such as cancer [8].

Several recent systematic reviews and/or meta-analyses have been inconclusive on the associations between (data derived and a priori) dietary patterns and pancreatic cancer risk [9–11]. Furthermore, associations between dietary patterns and pancreatic cancer were affected by the study design and gender composition of the cohort [9]. Hence, results from large prospective cohorts are imperative to improve the strength of the evidence linking diet and pancreatic cancer risk.

The United Kingdom Women's Cohort Study (UKWCS) is a large, high-quality cohort study among women. The UKWCS was carefully designed to explore links between diet and chronic disease, including cancer, avoiding typical errors and biases inherent in previous cohort studies that limit the ability to support dietary recommendations [12–15]. First, the cohort recruitment strategies ensured the representation of participants with a wide range of dietary patterns to maximize dietary variation. The cohort has similar and large numbers of participants in 3 main groups: vegetarian, fish, and meat-eaters. This design powers the cohort to explore potential relationships between diet (foods, nutrients, and dietary patterns) and cancer with high levels of confidence, improving its generalizability to women in the United Kingdom. The recruitment of participants with different dietary patterns into the UKWCS decreases measurement error bias and increases the power to detect diet–disease associations by ensuring sufficient variation of the exposure. Additionally, dietary intake in the cohort has been assessed by both a food frequency questionnaire (FFQ) and a 4-day food diary. This provides in-depth dietary data that are rarely available for cohort studies of similar size (with more than 30,000 participants). The UKWCS database also provides extensive documentation of lifestyle and demographic information and medical history data that allows for statistical adjustments in the analysis. Thus, the UKWCS cohort is uniquely positioned to critically evaluate the relationship between dietary factors and cancer risk. Our primary hypothesis was that specific dietary patterns would be associated with pancreatic cancer risk. We, therefore, aimed to evaluate the prospective associations between dietary patterns and pancreatic cancer risks in the women enrolled in the UKWCS over a 19-year follow-up period.

2. Methods and materials

2.1. *Settings and participants*

The recruitment and characteristics of the UKWCS participants have been described previously [13]. Briefly, the UKWCS is a prospective cohort that recruited 35,792 women

between 1995 and 1998. They were aged 35 to 69 years at baseline and lived in England, Wales, and Scotland. Women aged younger than 35 years or 70 years and above, and those who did not reside in England, Wales, or Scotland were excluded. A total of 35,372 women returned the baseline postal questionnaire. The baseline questionnaire collected sociodemographic data and information about participants' physical activity and comorbidities, among others.

2.2. Dietary intake assessment

The UKWCS participants' diet was assessed using a 217-item, self-administered FFQ based on that used in the Oxford arm of the European Prospective Investigation into Cancer study and adapted for use with vegetarians [13]. Completing the questionnaire required participants to place a tick in the box to indicate how frequently each food was consumed over the past year. Any missing items were assumed to have not been consumed. The FFQ data that provided information on the frequency and amount of intake of listed food of the individual participants collected at baseline were used to derive dietary patterns. Estimated caloric intake, macronutrient intake (absolute amount and percentage of calories from carbohydrate, protein, and fat), dietary fiber, and sugar intakes were also obtained from the UKWCS database.

2.3. Self-reported and a priori dietary patterns

At enrollment, the UKWCS participants had characterized themselves as vegans/vegetarians or omnivores [13]. This information was obtained to study the association of these eating habits with pancreatic cancer incidence. Diet quality scores of the participants at baseline were assessed using 2 predefined criteria: the Mediterranean diet score (MDS) and the World Health Organization-Healthy Diet Indicator (WHO-HDI) [12]. MDS indicates compliance with a traditional Mediterranean diet. The score comprises 10 significant indicators of adherence to the Mediterranean diet, and each participant was assigned a score of 0 or 1 for 9 of these components, using the cohort median as a cutoff. Intakes above the cutoff for vegetables, legumes, fruit and nuts, cereal, and fish and the ratio of monounsaturated fatty acids to saturated fatty acids each increased the score by 1. Intakes below the cutoffs for meat, poultry, and dairy products also increased the score by 1. For alcohol intake, the 10th component, women consuming between 5 and 25 g of alcohol per day increased their score by 1. Thus, total MDS scores ranged between 0 and 10.

The WHO-HDI scores were calculated based on adherence to WHO guidelines as described previously [12]. The score was modified considering dietary factors derivable from the FFQ used in the study. The HDI is measured from 0 to 10 by assigning a score of 1 if a woman's diet was within the recommended limits for the following components and 0 if otherwise. The 10 components scored include total carbohydrates, nonstarch polysaccharides, fruit and vegetable consumption, protein, cholesterol, nonmilk extrinsic sugars, salt, total fatty acids, saturated fatty acids, and polyunsaturated fatty acids. Total carbohydrates, nonstarch polysaccharides, fruit and vegetable consumption, protein, cholesterol, total fatty acids, saturated fatty acids, and polyunsaturated fatty acids were estimated from the FFQ. Nonmilk extrinsic sugars were estimated by subtracting sugar from fruit, vegetables, and milk from total sugar. Daily salt intake was calculated as total salt added during cooking and salt added at the table. Nevertheless, n-6 polyunsaturated fatty acids, n-3 polyunsaturated fatty acids, and trans fatty acids data were unavailable. Monounsaturated fatty acids were available; however, the difference between this component and the other fats was not estimable, and hence this component was not used as part of the score.

2.4. Derivation of a posteriori dietary patterns

Dietary patterns were generated from the FFQ using principal component analysis (PCA) with varimax rotation. Kaiser-Mayer-Olkin measurement was applied to evaluate PCA applicability. For ease of interpreting the patterns derived from the PCA [16,17], items from the FFQ were aggregated into 39 mutually exclusive groups (Supplemental Table S1). This aggregation was based on the similarity of food types and nutrient composition and finalized through consensus among the research team members who were nutritionists or dietitians. The food items in each of these categories are presented in Supplemental Table S1.

Five patterns were selected based on the scree plot, variation in diet attributable to a pattern, and interpretability of the pattern. Derived dietary patterns were labeled conventionally either based on the predominant foods consumed within a pattern or based on the healthiness of the pattern. Both negative and positive factor loading scores greater than 0.2 were considered. Foods with negative loading scores were reported as foods excluded and foods with positive loading scores as foods included within the dietary pattern.

To better characterize the dietary patterns, correlations between the dietary pattern scores obtained from PCA, and estimated calorie, macronutrient, and fiber intakes were explored. The dietary quality of the derived dietary patterns was evaluated by studying their correlation with the calculated WHO-HDI and MDS available in the UKWCS database.

2.5. Ascertainment of pancreatic cancer cases

Participants were flagged with the NHS Central Register for cancer and death notification. Incident cancers and causes of death were coded according to the International Classification of Diseases 9 and 10 (Supplemental Table S2). A documented medical diagnosis of pancreatic cancer from the linked Public Health England records was used as the outcome variable.

2.6. Ethics approval

The UKWCS has ethical approval as a research database (REC reference: 17/YH/0144) and a Public Health England data-sharing contract (ODR1718_148). For this specific analysis, institutional approvals were also obtained from the University of Leeds and the International Medical University (IMU) before the start of the project (IMU 435/2019). This paper is a data

analysis resulting from the permitted access to the UKWCS research database and does not require informed consent. The Integrated Research Campus of the University of Leeds holds the secure UKWCS data. For this analysis, data were accessed through a virtual research environment and handled according to the European Union General Data Protection Regulation requirements through institutional agreements between the University of Leeds and the IMU.

2.7. Sample size

With 136 cases of pancreatic cancer over 18.5 years of follow-up, the study had 80% power to detect a 40% reduction in risk from the Cox model (hazard ratio = 0.6) for 1 dietary pattern compared with another, assuming similar numbers in each and with the statistical significance set at $P < .05$.

2.8. Statistical analyses

To discern the interplay between food and nutrient intake and pancreatic cancer risk, we evaluated the relationship between pancreatic cancer incidence and (1) self-reported dietary pattern, (2) a priori diet quality indices, (3) FFQ data derived a posteriori dietary pattern generated using PCA. These relationships were explored using Cox proportional hazards regression survival analysis. The follow-up (person-years) for each participant was counted from the beginning of the study until the date of the pancreatic cancer diagnosis or the censor date (April 1, 2014), whichever occurred first.

The relationship of various dietary patterns with pancreatic cancer incidence was explored using two similar models. The first model was adjusted only for age in years (model 1). The second model additionally adjusted for smoking (reported nonsmokers/others) education (had degree, A and O levels/reported none of these qualifications), and physical activity level (as self-reported time spent on activities vigorous enough to cause sweating or a faster heartbeat [h/day]). This minimal set of adjustments was identified using DAGitty, a web-based software for analyzing causal diagrams [18] (Supplemental Fig. S2). Linear trends associating a priori and a posteriori dietary patterns with pancreatic cancer risk were explored, treating the exposure as continuous variables. Self-reported dietary patterns were dichotomous variables and used accordingly in the analysis. The relationships are expressed as hazard ratios with 95% confidence intervals (CI). Because of the small amount of missing data, no imputations were undertaken to address missing data.

Two additional sensitivity analyses were performed to exclude reverse causality: (1) removing participants who were censored or were diagnosed with pancreatic cancer within 3 years of enrollment to account for latent pancreatic cancer cases at enrolment and (2) excluding all participants with diabetes at enrollment to account for diabetes as a symptom of pancreatic cancer.

All statistical analysis was conducted using STATA version 16 (Stata Corp. 2017; Stata Statistical Software: Release 15; College Station, TX: Stata Corp LLC.) and $P < .05$ was considered statistically significant.

Table 1 – Dietary intake characteristics of the United Kingdom Women's Cohort Study participants at enrollment

Dietary intake characteristics	
Self-reported dietary practices	(n = 35,364)
Vegan or vegetarian, n (%)	9830 (28%)
Daily energy and macronutrient intake[a]	(n = 35,026)
Energy intake (kcal)	2291 (798)
Protein (g)	90 (32)
Carbohydrate (g)	313 (112)
Fat (g)	85 (36)
Saturated fat (g)	29 (14)
Monounsaturated fat (g)	28 (13)
Polyunsaturated fat (g)	16 (8)
Fiber (g)	26 (11)
Sugar (g)	150 (64)

[a] Data expressed as mean (SD).

3. Results

3.1. Characteristics of the participants at enrollment

For the current analysis, 35,365 participants with a mean follow-up duration of 18.5 years (range = 0.05-21.21 years) were available for this analysis, excluding 15 participants with pancreatic cancer at enrollment. The follow-up accounts for 654,566.3 person-years, and 136 incident pancreatic cancer cases were recorded during the follow-up. Thus, the incidence rate of pancreatic cancer in the UKWCS was 0.21 per 1000 person-years.

The demographic characteristics of the participants included in the analysis have been published previously [19]. In brief, participants at enrollment had a mean (standard deviation [SD]) age of 52 (9) years, with 53% (n =17,781) of the participants being postmenopausal. Most participants had an education above O-Level (equivalent to Grade10 in American schools, n = 29,847, 84%). At enrollment, 11% (n = 3810) of the participants were smokers and participants' self-reported participation in vigorous activity ranged from 0 to 14 h/day, with a mean (SD) of approximately 15 (29) minutes per day.

The mean (SD) body mass index (BMI) at enrollment was 24.5 (4.3) kg/m^2, with 60% (n = 21,300), 25% (n= 8628), and 10% (n = 3359) of the participants categorized as having normal weight (18.5-24.9 kg/m^2), overweight (25.0-29.9 kg/m^2), and obesity (>30.0 kg/m^2), respectively. Two percent (n = 644) of the participants reported having diabetes at baseline.

3.2. Dietary intake of the participants at enrollment

The energy and macronutrient intakes of the participants at enrollment are summarized in Table 1. Overall mean (SD) energy intake among the participants of the UKWCS was 2291 (798) kcal, with 53%, 15%, and 32% of the proportion of calories coming from carbohydrates, protein, and fat, respectively.

A total of 9830 (28%) participants reported being vegans/vegetarians, with the rest identifying themselves as omnivores. The distribution of WHO-HDI and MDS in the UKWCS population is presented in Fig. 1. The mean (SD) WHO-HDI

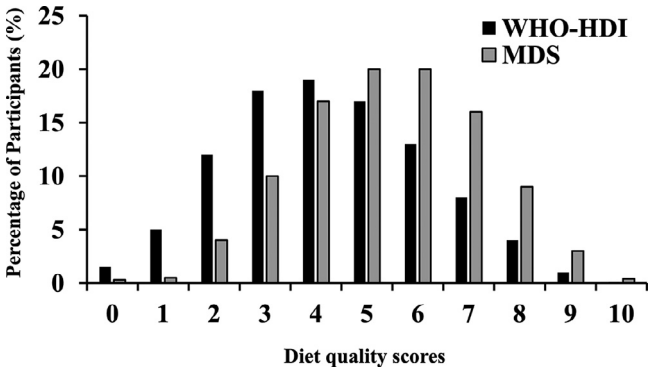

Fig. 1 – Distribution of diet quality scores in the United Kingdom Women's Cohort Study showed low to moderate diet quality in the majority of study participants. Less than 50% of the participants scored more than 5 out of the maximum possible score of 10 for either diet quality index, indicating poor to moderate diet quality in a substantial proportion of the cohort. Scores ranged from 0 to 10. MDS, Mediterranean diet score; WHO-HDI, World Health Organization-Healthy Diet Indicator.

scores and MDS of the participants of the maximum possible score of 10 for both scores were 4.27 (1.92) and 5.43 (1.76), respectively. Less than 50% of the participants scored higher than 5 for either diet quality index, indicating poor to moderate diet quality in a substantial proportion of the cohort.

3.3. *Data-derived dietary patterns*

Five major dietary patterns were identified from the UKWCS FFQ data using PCA. The scree plot for this analysis is shown in Supplemental Fig. S1. The 5 patterns were sufficiently distinct, and each pattern loaded highly on a range of nonoverlapping food items. These patterns were labeled as: "prudent,'' "meat-based," "fast food-sugar sweetened beverages-carbohydrate-rich-snack," "ready-to-eat cereal and dairy-rich," and "low diversity-lowfat" patterns. The dietary patterns and their characteristics are shown in Table 2. Together, these 5 patterns explained 44% of the total dietary variation within the cohort.

3.4. *Characterizing the dietary patterns*

Participants who self-reported adherence to vegan or vegetarian dietary patterns had significantly higher mean (95% CI) HDI (5.4 [5.3-5.4] vs. 3.8 [3.8-3.8]; $P < .001$) and MDS (6.6 [6.5-6.6] vs. 4.96 [4.9- 5.0]; $P < .001$) compared with those who did not identify themselves as vegan or vegetarians at enrollment.

Correlations between diet quality indices, data-derived dietary pattern scores, and macronutrient intakes are shown in Fig. 2. Higher adherence to the "prudent" dietary pattern was associated with better diet quality scores. All other data-derived dietary patterns in the UKWCS population showed a negative or negligible correlation with diet quality scores. The meat-based dietary pattern was the least correlated with diet quality scores. Among the data-derived dietary patterns, "prudent" (DP1) and "ready to eat-cereal and dairy-rich" (DP4) patterns scores were moderately positively correlated with caloric intake. Meat-based dietary pattern (DP2) correlated positively with protein intake, and the "fast food-sugar sweetened beverages-carbohydrate-rich snack-based" pattern (DP3) correlated with fat intake. Although "prudent" and "ready to eat cereal and dairy-rich" patterns were associated with dietary fiber intakes; meat-based dietary pattern scores were negatively associated with fiber intake.

Although higher adherence to the meat-based dietary pattern was correlated with older age (r [95% CI]: = 0.21 [0.20-0.22]), adherence to fast-food-sugar-sweetened beverages-carbohydrate-rich snacks was correlated with younger age of the participants (r = –0.36 [–0.37 to –0.35]). No significant correlation with the age of the participants was noted for the other dietary patterns.

3.5. *Dietary patterns and pancreatic cancer risk in the UKWCS*

The association between dietary patterns at enrolment and the incidence of pancreatic cancer in the UKWCS is shown in Table 3. There was no evidence of an association between dietary patterns (self-reported vegan or vegetarian dietary patterns, a priori or data-derived) and pancreatic cancer risk in this analysis. These findings remained unaltered in the sensitivity analysis when latent cases of pancreatic cancer at baseline were excluded from the analysis (Supplemental Table S3) or when participants with diabetes were excluded from the analysis (Supplemental Table S4).

4. Discussion

This analysis investigated the association of self-reported vegan and vegetarian eating patterns, 2 diet quality indices (a priori dietary patterns) and data-derived a posteriori dietary patterns with pancreatic cancer risk. Despite the unique construction of the UKWCS cohort allowing for sufficient variation in dietary exposure [13] for the exploration, there was no evidence to indicate any of these patterns was associated with pancreatic cancer incidence.

Self-reported vegans or vegetarians had higher dietary quality in this analysis. A previous analysis of the UKWCS data had shown that women with higher concordance to the a priori dietary patterns (i.e., better diet quality) were younger. Additionally, women with the highest WHO-HDI and MDS scores had a lower BMI, were less likely to smoke, and had higher physical activity levels [12,20]. However, higher WHO-HDI scores or MDS did not reduce breast cancer risk [12] or, in the current analysis, pancreatic cancer risk among UKWCS participants. Among the diet quality metrics, the WHO-HDI has very limited evidence linking it to reduced risk of noncommunicable diseases, including cancer [21]. A recent effort that synthesized and graded the quality of evidence for several diet quality metrics and their validity for predicting disease risks in various populations also found no evidence linking WHO-HDI to pancreatic cancer risk [21].

Meanwhile, the lack of association between MDS and pancreatic cancer risk seen in the current analysis agrees with the findings from a pooled analysis of 2 Dutch cohorts. The

Table 2 – Characteristics of the 5 major dietary patterns in the United Kingdom Women's Cohort Study

Dietary pattern Label	1 Prudent	2 Meat-based	3 Fast food-SSB-carbohydrate-rich snacks	4 Ready to eat-cereal and dairy rich	5 Low diversity-lowfat
Foods – high intakes (factor loading scores > 0.2)	GLV, other vegetables, cruciferous vegetables, fruits, legumes, root vegetables, whole grains, and dried fruit	Processed meat, beef-lamb-pork, offal, poultry, fish and seafood, fish products	Fried snacks, fast food, refined carbohydrates, alcoholic beverages, condiments, SSB, oily spreads, cheese and cheesy food	Carbohydrate-rich-snacks, sugary spreads, breakfast cereal, dairy full fat, chocolate-malt beverages, sweet confectionery, dried fruit, butter and substitutes	Spreads oily lowfat, dairy lowfat, SSB, condiments
Foods – excluded (negative factor loading scores <–0.2)	Refined carbohydrates, beef-lamb-pork, chocolate and malted beverages, SSB, carbohydrate-rich snacks, fried snacks, sweet confectionary	Sugary spreads, carbohydrate-rich snacks, breakfast cereal, sweet confectionary, chocolate and malted beverages, fried snacks, tea, dried fruits, condiments, other vegetables, cheese and cheese products, legumes, nuts and seeds, whole grains, spreads and soy foods	Wholegrains, chocolate and malted beverages, dairy-lowfat, GLV, fish and seafood, tea, cruciferous vegetables, breakfast cereal, fruits, sugary spreads, dried fruits	Beef-lamb-pork, fast food, fish and seafood, spreads oily-low fat, fried snacks, legumes, offal, cruciferous vegetables, oily spreads, GLV, other vegetables, alcoholic beverages	Soy foods, legumes, beef-lamb-pork, juice, fish and seafood, fried snacks, dried fruit eggs, offal, whole grain, spreads-oily, dairy-full-fat, soup, tea, alcoholic beverages, sugary spreads, nuts and seeds, spreads, butter and substitutes
Dietary variation explained (%)	12	11	8	7	5

Abbreviations: GLV, green leafy vegetables; SSB, sugar-sweetened beverages.
Dietary patterns derived using principal component analysis

Dutch cohort data showed that higher adherence to MDS was not associated with pancreatic cancer risk and that these findings remained unaffected by sex and type of MDS used [22]. Our findings and those from Schlupen et al. [22] contradict trends reported by other case-control [23]and cohort studies [24,25]. Zheng et al. [9], in their systematic review of dietary patterns associated with pancreatic cancer risk, observed that although case-control studies showed a beneficial effect of higher adherence to MDS in protecting against pancreatic cancer risk, the association was not observed in cohort studies. Schlupen et al. [22] posit that dietary changes from the presence of preclinical disease account for the inverse association observed in the case-control studies in the absence of a true effect. Dietary changes in case-control studies could likely have captured changes in dietary intake that are secondary to the disease. It is unclear if cancer itself or the treatment could have altered dietary intakes and caused these spurious associations between diet and disease. This bias, attributed to the case-control study design, is avoided in prospective cohort studies, including the UKWCS. Moreover, to account for any undiagnosed preclinical disease that could have affected the results, we performed a sensitivity analysis removing latent pancreatic cancer cases and participants with diabetes at enrollment. The results of these sensitivity analyses agreed with the primary analysis. However, it also noted the number of pancreatic cancer cases was small [9] and could potentially explain the lack of evidence of association in cohort studies, including ours. Nevertheless, the cohort with a considerably higher number of pancreatic cancer cases ($n = 838$ among females) also found no evidence of an association between diet quality index (Healthy Eating Index) and pancreatic cancer risk when adjusted for potential confounders [26].

Our findings add to the existing evidence indicating the lack of robust associations between data-driven dietary patterns and pancreatic cancer risk in cohort studies [9]. Higher adherence to "prudent diets" with high intakes of fruits and vegetables was not associated with a reduced risk of pancreatic cancer in an analysis of data from 2 large prospective cohort studies that included male and female participants [27]. This analysis included participants of the Health Professionals Follow-Up Study and the Nurses' Health Study in the United States. The study reported that stratifying by BMI or physical activity did not affect the observed association. Similarly, the Iowa Women's Health Study that followed up a large cohort of postmenopausal women found no significant associations between intake of nutrients and food groups or dietary patterns and pancreatic cancer [28]. A case-control approach using pooled data from various cohorts from the United Kingdom, including the UKWCS by the UK Dietary Cohort Consortium, found no associations between PCA-derived dietary pat-

Dietary Pattern	Kcal	CHO (g)	Protein (g)	Fat (g)	SFA(g)	MUFA(g)	PUFA(g)	Fibre(g)	Sugar(g)	WHO-HDI	MDS
Diet quality indices											
WHO-HDI	-0.1	0.1	-0.2	-0.3	-0.4	-0.3	0	0.4	0.1	NA	0.5
MDS	0.2	0.3	0	0.1	-0.1	0.1	0.3	0.5	0.2	0.5	NA
Data-derived dietary patterns											
DP1: Prudent	0.4	0.4	0.4	0.3	0.1	0.3	0.5	0.6	0.4	0.3	0.6
DP2: Meat-based	0.1	0	0.4	0.2	0.3	0.2	0	-0.2	0	-0.5	-0.4
DP3: Fast food- SSB-carb-rich snacks	0.4	0.3	0.3	0.5	0.5	0.5	0.4	0.1	0.2	-0.2	0.1
DP4: Cereal rich- dairy	0.6	0.6	0.5	0.6	0.6	0.6	0.4	0.4	0.6	-0.2	0.1
DP5: Low diversity- low fat	0.1	0.2	0.2	-0.1	-0.1	-0.1	-0.1	0.1	0.2	0.1	-0.1

Fig. 2 – Strength of correlation between diet quality indices, data-derived diet pattern scores and macronutrient intakes in the United Kingdom Women's Cohort Study. DP 1 to 5 indicates data-derived dietary patterns 1 to 5. Color coding in the table denotes the direction and magnitude of correlation. The color map moves from black, indicating the strongest negative correlation, to white, highlighting the strongest positive correlation. Intermediate correlations are shown in gray. The closer the shading is to white or black, the greater the magnitude of the correlation coefficient. Higher adherence to the "prudent" category was the only dietary pattern associated with better diet quality scores. DP, dietary pattern; MDS, Mediterranean Diet Score; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids; SFA, saturated fatty acids; WHO-HDI, World Health Organization Healthy Diet Indicator.

terns and breast cancer risk [29]. In addition, the association between diet and pancreatic cancer are predominantly seen in men but not women [9].

Although our analysis showed no evidence that associated dietary patterns with pancreatic cancer risk, we have previously shown that obesity is a significant predictor of pancreatic cancer incidence [19]. Diet is a common modifiable risk factor for obesity. Therefore, dietary patterns preventing excessive weight gain could reduce pancreatic cancer risk. The WHO-HDI and MDS were inversely associated with BMI in this cohort of women [13]. Both meat-based and low-diversity, low-fat dietary patterns had negative loading for nuts. Nut intake was associated with lower body weight [30]. The meat-based dietary pattern also showed significant inverse correlations with both the WHO-HDI and MDS with a poor loading for fruits and vegetables. Future work could explore how diet interacts with body weight in relation to risk of pancreatic cancer. Potentially using new online tools to collect detailed dietary data that may reflect intakes more specifically than FFQs used, to date, in cohort studies [31]. This would allow development of individualized dietary advice to optimize dietary quality.

We then deliberated if the lack of association of data-derived dietary patterns with pancreatic cancers in the current analysis could be attributed to the limitations of the PCA method. Although the subjectivity involved in the process has been acknowledged as a potential limitation, PCA is a commonly used method to characterize the dietary pattern in a population [32]. To verify our PCA-derived dietary patterns, we compared our results with those previously reported using the UKWCS data. An earlier study used k-cluster analysis to derive dietary patterns in the UKWCS [33]. This analysis derived 7 dietary patterns that were labeled as "monotonous low-quantity omnivore, health conscious, traditional meat, chips, and pudding eater, higher diversity traditional omnivore, conservative omnivore, low-diversity vegetarian, high-diversity vegetarian." Certain similarities between the dietary patterns derived in this study and ours are observable. For instance, overlaps in the food consumption patterns are apparent between the "health conscious, traditional meat, and low-diversity vegetarian" patterns reported previously and the "prudent, meat-based, and low-diversity lowfat" patterns derived in the current study, respectively.

These overlaps indicate adequate reproducibility of dietary patterns derived using PCA in the cohort. Additionally, although the dietary patterns derived in the current analysis explained 44% of the variation in the diet in the UKWCS, the PCA attempted by the UK Dietary Cohort Consortium [29] explained only 6.2% of the variation in dietary intakes in the pooled samples. Thus, the subjective food categorization decisions used before performing the PCA undertaken in the current analysis seem relevant and appropriate to the UKWCS population.

The PCA method derives the dietary patterns in a population independent of health outcomes. Thus, the lack of association between data-derived dietary patterns and pancreatic cancer risk across studies could reflect that the existing dietary patterns in populations may not necessarily be healthy. In the current analysis, less than 50% of the participants had WHO-HDI or MDS results >50%, indicating overall poor-moderate dietary quality. A careful analysis of food group clustering in Table 2 shows poor loading for fruits and vegetables in 4 of the 5 derived dietary patterns. The lack of

Table 3 – Diet pattern scores (derived from PCA) and HR (95% CI) for pancreatic cancer in the United Kingdom Women's Cohort Study

	Age-adjusted model HR (95% CI)	P value	Fully adjusted model[a] HR (95% CI)	P value
Self-reported diet patterns				
Vegan or vegetarian diet pattern				
Cases/total	124/32,975		118/31,293	
Self-reported vegan or vegetarian	Ref	.48	Ref	
Omnivores (not vegan or vegetarian)	1.16 (0.76-1.79)		1.13 (0.73-1.76)	.58
A priori diet patterns (diet quality indices)				
Cases/total	136/34,945		128/33,084	
WHO-HDI score				
Linear (per unit score increase)	0.98 (0.90-1.07)	.68	0.99 (0.91-1.09)	.89
Mediterranean diet score				
Linear (per unit score increase)	0.93 (0.84-1.02)	.13	0.92 (0.83-1.02)	.16
Posteriori diet patterns (data-derived)				
Cases/total	136/ 34,945		128/ 33,084	
Diet pattern 1 "prudent"				
Linear (per SD)	0.99 (0.92-1.07)	.87	1.02 (0.94-1.10)	.69
Diet pattern 2 "meat-based"				
Linear (per SD)	1.02 (0.94-1.11)	.64	1.00 (0.92-1.09)	.97
Diet pattern 3 "fast-food, sugar-sweetened beverages, and carbohydrate-rich snacks"				
Linear (per SD)	0.98 (0.88-1.09)	.75	0.96 (0.86-1.07)	.44
Diet pattern 4 "cereal and dairy rich"				
Linear (per SD)	1.04 (0.95-1.15)	.40	1.04 (0.94-1.16)	.40
Diet pattern 5 "low-diversity and lowfat"				
Linear (per SD)	1.02 (0.91-1.15)	.72	1.00 (0.89-1.13)	.95

Abbreviations: CI, confidence interval; HR, hazard ratio; PCA, principal component analysis; SD, standard deviation; WHO-HDI, World Health Organization-Healthy Diet Indicator.
Posteriori diet patterns (data-derived) using principal component analysis.
[a] Fully adjusted model : adjusted for age, smoking, education, and physical activity level. Missing data: age, 1.2%, physical activity (5.8%). None missing for education and smoking.

correlation or inverse correlations between the majority of the dietary patterns and the diet quality indices further suggests that several major dietary patterns in the cohort fell short of nutrient adequacy and dietary diversity.

The current analysis has several strengths that include its large sample size, the construct of the UKWCS cohort that allowed for representation of varying dietary patterns, and the prospective study design with sufficiently long follow-up. The single-gender cohort also allows for the elimination of sex differences in the effect of overall dietary patterns on pancreatic cancer risk, which remains poorly understood [9]. This is especially important because of the potential implication of sex hormones, though the evidence is controversial [34–38]. The use of a women-only cohort is also further justified in that in the United Kingdom, there is an almost equal distribution of pancreatic cancer cases between the sexes and between 2017 and 2019, whereas the pancreatic cancer mortality rates in females have increased by 12% the rates have decreased by 12% in men [39]. Also, we analyzed dietary patterns using 3 methods: self-reported, diet quality combination indices that measured both dietary diversity and nutrient adequacy, and, finally, data-derived dietary patterns to describe the major eating patterns in the cohort.

Nevertheless, we acknowledge certain limitations that could have attenuated any true relationship between diet and pancreatic cancer risk in this analysis. First, the cohort had limited pancreatic cancer cases. The incidence rate of pancreatic cancer in the UKWCS was 21 cases per 100,000, which is similar to or slightly higher than the 17 cases/100,000 reported by Cancer Research UK [39]. However, the incidence of pancreatic cancer is much lower compared with the more common types of cancer such as breast cancer (170/10,000) or bowel cancer (70/100,00) [40]. Therefore, given the rarer nature of the disease, despite the large sample size of the UKWCS, the study could still be underpowered for smaller associations and a larger sample size would be required to detect smaller associations between dietary patterns and pancreatic cancer risk. Second, dietary intake and physical activity were self-reported, which makes the estimates prone to measurement errors and misclassification [13,41]. FFQs also fail to capture information that may be important in the etiology of cancer, such as cooking methods, the presence of food additives, and contaminants [28]. The lack of n-6 and n-3 polyunsaturated fatty acids data to calculate relative intake of monounsaturated fatty acids/other fats also limits the accuracy of the calculation of the WHO-HDI score. Additionally, the women in the UKWCS were also healthier than the average British woman [13], which is likely to have reduced any diet–disease relationship. Finally, the role of residual confounding in attenuating the diet–disease relationship cannot be discounted.

Importantly, dietary patterns and lifestyle habits in the cohort may have changed over time, and this analysis does not account for the effect of these changes. A previous evaluation in the UKWCS showed that dietary patterns had moderate stability over a 5-year period in this cohort [42]. These findings showed that evaluation of dietary patterns in comparison to studying single nutrients or energy intakes minimized exposure misclassification arising from changes over time. Nevertheless, a longer longitudinal evaluation of dietary changes during adult life in the United Kingdom found fair-to-moderate stability for fruits, vegetables, dairy, and mixed dietary patterns between 1982 and 1999. Over these 17 years, the "meat, potatoes, and sweet foods" dietary pattern in women showed poor stability [43]. Interestingly, the National Diet and Nutrition Surveys conducted between 2000 to 2001 and 2008 to 2009 showed no changes in energy, total fat, or carbohydrate intakes. Between the 2 surveys, there were no major changes in the intake of cereals, fruits and vegetables, or sugar, preserves, confectionary, and savory snacks in adults. During this period, however, whole milk and potato consumption decreased and intakes of reduced-fat spreads, meat, and meat products increased among adults [44]. A large part of the follow-up period of the UKWCS coincides with the period evaluated by Whitton et al [44]. Thus, it is likely that there were some changes in the dietary patterns of the cohort participants during the follow-up.

Given the limitations we have observed while evaluating diet–disease relationships in the current analysis, recommendations to improve studies in nutritional epidemiology should be carefully considered when designing future research [45–48]. Dietary assessment needs to be improved. The most agreed on and feasible improvement for adoption in future prospective studies would be the use of repeated 24-hour dietary recalls throughout the follow-up period that would better document changes in dietary intake over time and capture seasonal variations, if any. Moreover, updating food composition databases to have a wider coverage of foods and nutrients, though time-consuming and expensive, will provide better underlying data to help characterize diet–disease relationships. Other recommendations suggest various degrees of automation including the use of internet-based dietary logging, optimizing data capture from user-generated food photos, and/or the use of integrated software systems with built-in food composition databases that automate dietary and nutrient intake estimation to improve the accuracy of dietary intake estimation. Additionally, harnessing multi-omic technologies in nutritional epidemiology will facilitate the personalization of dietary recommendations by characterizing variations in dietary response based on several individual characteristics including genotype, phenotype, lifestyle, and gut microbiota [49].

5. Conclusion

In this prospective cohort of middle-aged UK women, we analyzed the relationship between dietary patterns and pancreatic cancer risk. We uniquely characterized dietary patterns using 3 complementary methods: self-reported dietary habits (self-reported vegan or vegetarian patterns), diet quality indicators (WHO-HDI and MDS), and data-derived dietary patterns in the cohort. Major dietary patterns in the cohort were often of poor dietary quality. The commonly consumed dietary patterns at baseline showed no evidence of association with pancreatic cancer incidence over a median of 19 years.

Declaration of Competing Interest

Janet Cade is the Director of Dietary Assessment Ltd. The other authors declare no relationships that could be construed as potential conflicts of interest.

CRediT authorship contribution statement

Sangeetha Shyam: Conceptualization, Methodology, Formal analysis, Funding acquisition, Visualization, Writing – original draft. **Darren C. Greenwood:** Conceptualization, Methodology, Validation, Data curation, Investigation, Supervision, Formal analysis, Writing – review & editing. **Chun-Wai Mai:** Conceptualization, Visualization, Writing – review & editing. **Seok Shin Tan:** Conceptualization, Visualization, Writing – review & editing. **Barakatun-Nisak Mohd Yusof:** Conceptualization, Visualization, Writing – review & editing. **Foong Ming Moy:** Conceptualization, Visualization, Writing – review & editing. **Janet E. Cade:** Conceptualization, Resources, Methodology, Validation, Investigation, Supervision, Project administration, Funding acquisition, Writing – review & editing.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.nutres.2023.07.007.

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