PAPER

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Adherence to the Mediterranean diet is associated with reduced chronic pancreatitis risk: a longitudinal cohort study†

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Background: The role of diet on the risk of chronic pancreatitis (CP) is understudied. The health benefits of the Mediterranean diet (MedDiet) pattern have long been recognized, but its association with CP risk is unclear. We aimed to investigate the association between adherence to MedDiet and the incidence of CP in a large-scale cohort. *Methods*: 190 790 participants from the UK Biobank were involved, all free of CP and with typical diet recall data at recruitment. The diagnosis of CP was ascertained by the combination of hospital inpatient data, primary care data, and death registry data. Multivariable Cox regression models were used to evaluate the associations between MedDiet adherence, measured by the Mediterranean Diet Adherence Screener (MEDAS) continuous score, and the incidence of CP. The mediating role of inflammation (assessed by C-reactive protein) and metabolic status between MedDiet adherence and CP risk was also investigated. *Results*: During a mean of 10.8 years of follow-up, 214 participants developed CP. Individuals with the highest adherence to MedDiet, defined by continuous MEDAS scores, exhibited significantly lower risk of developing CP (hazard ratio [HR] = 0.57, 95% confidence interval [CI]: 0.40–0.82; p = 0.002) compared to those in the lowest tertiles. Metabolic status mediated 4.74% of the association between MedDiet adherence and CP risk, while the mediating role of C-reactive protein was not significant. *Conclusion*: Greater Mediterranean diet adherence is associated with reduced chronic pancreatitis risk.

1. Introduction

Chronic pancreatitis (CP) is a pathologic fibro-inflammatory syndrome of the pancreas in individuals with genetic, environmental and/or other risk factors who develop persistent pathologic responses to parenchymal injury or stress.[1] It is characterized by persistent abdominal pain, chronic endocrine and/or exocrine pancreatic insufficiencies, and life-threatening long-term complications including diabetes and pancreatic cancer.[2,3] The impact of CP on patients' quality of life and economic burden is significant.

Available treatments primarily focus on relieving symptoms and managing complications, while surgical intervention is recommended only for patients who have exhausted all medical options.[4] This highlights the need to identify modifiable risk factors for preventing the disease. Over recent years, the incidence of CP has increased worldwide,[5] while its risk factors remain poorly defined. Excessive alcohol consumption is identified as the single most common cause of CP.[3] Other major risk factors include smoking and genetic predisposition. Nutritional factors receive limited attention in current guidelines addressing the etiology of the disease, with notable findings primarily found in the M-ANNHEIM multiple risk factor classification system, which provides a framework for evaluating various risk factors.[4,6] The acronym stands for (A) alcohol consumption, (N) nicotine consumption, (N) nutritional factors, (H) hereditary factors, (E) efferent duct factors, (I) immunological factors, and (M) miscellaneous and rare metabolic factors.[7] However, the available literature on the role of diet primarily consists of limited cross-sectional studies focused on individual foods and nutrients, resulting in inconclusive findings.[8–15] Since nutrients and foods are consumed in combination and may have synergistic or antagonistic

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effects, analyzing overall dietary patterns may provide a more comprehensive approach to disease prevention.[16] Investigating dietary patterns as a whole in the development of CP is warranted.

The Mediterranean diet (MedDiet) is one of the most studied and well-known dietary patterns globally,[17,18] characterized by high consumption of olive oil, vegetables, legumes, fruits and nuts, cereals, and seafood, alongside reduced intake of red meat, dairy products, saturated fats, and moderate intake of wine with meals.[19,20] Abundant in antioxidant and anti-inflammatory molecules,[21] this dietary pattern has been reported to offer significant protection against various diseases linked to chronic low-grade inflammation.[22,23] Furthermore, research has explored its effectiveness in preventing various digestive disorders, such as gastrointestinal disorders and chronic liver diseases,[24,25] which may share certain etiological bases with CP. Given its established benefits in these areas, it is reasonable to expect a protective role for MedDiet in the etiology of CP. However, to date, no large-scale cohort studies have evaluated the association between MedDiet adherence and CP incidence. Our study aims to fill this research gap by investigating the association between MedDiet adherence and the risk of developing CP in the UK Biobank cohort.

2. Methods

2.1 Study design and participants

The UK Biobank is a large prospective cohort involving half a million UK participants aged between 40 and 69 at the time of enrollment during 2006–2010. The baseline assessment included a touchscreen questionnaire, a brief interview, physical measurements, and biological samples. In addition, a range of additional assessments was conducted, including a 24-hour dietary Web questionnaire.[26] Through linkages to a range of national datasets including primary care, inpatient hospital admissions, and death registries, the UK Biobank can routinely follow up the health outcomes of all participants who were registered with a general practitioner in the National Health Service (NHS) and had consented to the process.[27] Ethical approval for the UK Biobank study was granted by the North West–Haydock Research Ethics Committee (REC reference 16/NW/0274).

The current study included participants who were free of CP at recruitment and completed at least one 24-hour questionnaire. To minimise measurement error, we further excluded diet recalls reported as non-typical days, and those with typical diet recalls and plausible energy intake (800–4200 kcal for men and 600–3500 kcal for women[28]). To reduce potential reverse causality, participants who developed CP within two years after recruitment ($n = 38$) were excluded. A total of 190 790 participants were included in this study (Fig. 1).

2.2 Exposure assessment

Dietary intake. Data on dietary intake were collected from a subset of UK Biobank participants involving over 200 000 participants.[26] The assessment was conducted using Oxford WebQ, an online 24-hour dietary assessment tool developed for large prospective studies.[29,30] It has been validated and showed comparable validity to interviewer-based 24-hour recall methods, with Spearman's correlation ranging from 0.5 to 0.9 for major nutrients.[29,31] The questionnaire covers the consumption of up to 206 commonly consumed foods and 32 types of drinks during the previous 24 hours. Participants were prompted to choose the food items they consumed and specify the number of standard portions. Food intake in grams was calculated automatically through the multiplication of consumed amounts by the standard portion size specified in standard United Kingdom food composition tables.[32]

Up to a total of five assessments had been finished, including a baseline assessment between April 2009 and September 2010, and four additional assessments *via* email invitations
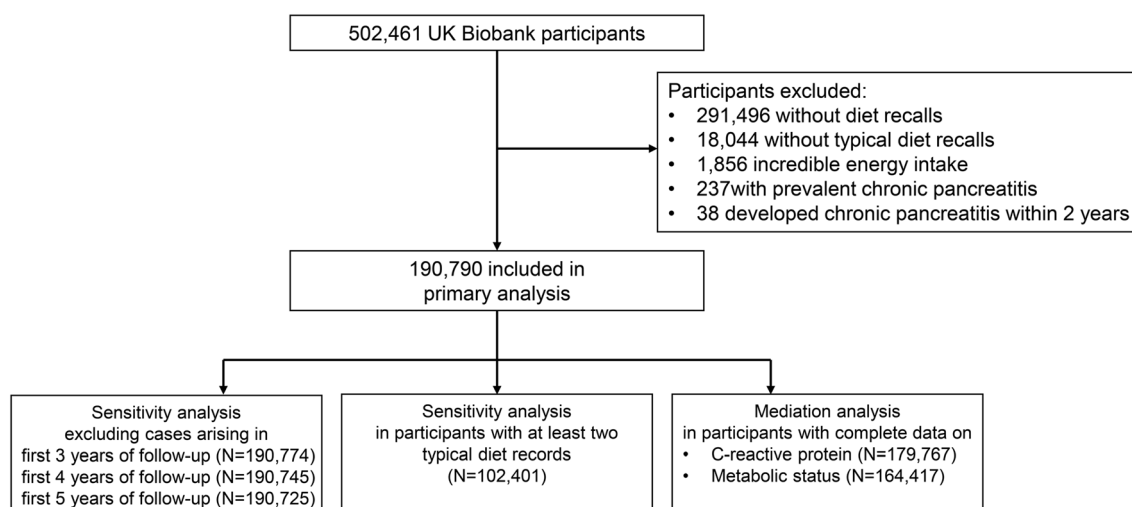

Fig. 1 Flowchart of the study showing participants' inclusion in the primary analysis, sensitivity analysis, and mediation analysis.

between February 2011 and June 2012.[28] For participants with more than one typical diet recall, we used the mean intake of these multiple measurements for those who completed the assessment two or more times to better capture their typical intake.

Mediterranean diet adherence. The MedDiet adherence screener (MEDAS) continuous score was used to assess MedDiet adherence, given its greater sensitivity in detecting differences in diet quality.[33] Developed by Shannon *et al.*[33], the MEDAS continuous score is based on the standard binary MEDAS score, a brief 14-item questionnaire validated for application in UK populations.[34] Both versions require participants to report their habitual consumption of 12 primary components of the Mediterranean diet and 2 related food habits, with higher scores reflecting higher MedDiet adherence. For the binary MEDAS score, participants receive either 0 or 1 point for each of the 14 items, based on whether they meet the specified cut-off. By contrast, the MEDAS continuous score assigns points on a continuous scale from 0 to 1, reflecting the degree of adherence to the dietary target.[33,35] As described in a previous study,[36] the MEDAS continuous score is calculated using the linear equation principle. For instance, one target item involves consuming three or more servings (150 g per serving) of legumes per week. An individual consuming 300 g of legumes weekly would receive 0 points in the MEDAS binary score for not meeting the 3-serving target (*i.e.*, 450 g). In contrast, in the MEDAS continuous score, a score of 0.67 points would be assigned, reflecting the proximity to the target (approximately 2/3 of the way). Full details of scoring methodologies are provided in ESI Tables S1 and S2.†

In this study, two adjustments were made to the original 14-item scoring system. Firstly, one target item requiring a specific amount of olive oil intake (four or more tablespoons daily) was excluded due to the unavailability of dietary data. This issue was also examined in prior research.[36] Previous findings indicate that few individuals in a UK setting consume enough olive oil to score a full point, suggesting a limited impact on our overall scores.[33] Secondly, given alcohol consumption is the primary risk factor for CP, the wine category was adapted by assigning 1 point for no alcohol intake and 0 points for any alcohol intake. The alcohol consumption documented in the UK Biobank includes rose, red, and white wine, beer/cider, fortified wine, spirits, and other alcohol intake (ESI Table S2†). The residual method was employed to compute energy-adjusted scores by regressing the diet quality score against total energy intake.[37,38]

2.3 Outcome ascertainment

The identification of all-cause CP in the UK Biobank came from the nationwide hospital inpatient data, primary care data, as well as death registry data. As with previous studies,[39–41] based on the study timeframe, an International Classification of Diseases (ICD) code was used in hospital inpatient data (ICD-9: 577.1; ICD-10: K86.0, K86.1) and death registry data (ICD-10: K86.0, K86.1). The primary care records employed both Read v2 and Read v3, which were subsequently mapped to ICD codes (ESI Table S4†). All current UK Biobank-linked inpatient hospital admissions, death registries, and primary care data are available for a total of approximately 45% of the cohort. Considering the long-term and progressive nature of chronic pancreatitis, hospital admissions and death registries serve as the primary sources for outcome ascertainment, so the information missed by general practitioners is likely minimal. According to the UK Audit Commission, the overall accuracy of disease identification using ICD codes can be as high as 89%.[42]

2.4 Covariates

The covariates were chosen based on prior knowledge and previous studies.[43,44] These covariates included age (continuous), sex (male/female), ethnicity (white/others), Townsend deprivation index (TDI; low, moderate, high deprivation), education level (below college/college and above), smoking status (never, previous, current), physical activity (low, moderate, high intensity), body mass index (BMI; <25 kg m^{-2}, 25–29.9 kg m^{-2}, >30 kg m^{-2}), Charlson Comorbidity Index (CCI; continuous), sleep duration (continuous), baseline diabetes (no/yes) and total energy intake (continuous in kcal d^{-1}).

TDI was used to assign socioeconomic status, calculated based on the national census output areas corresponding to participants' postcodes.[45] Higher scores of TDI indicate greater levels of deprivation. Physical activity was evaluated using adapted inquiries derived from the short version of the International Physical Activity Questionnaire (IPAQ).[46] BMI was defined as body mass divided by the square of the body height (kg m^{-2}). CCI scores were computed based on 17 comorbidities, each assigned a weighted value according to their severity and mortality risk.[47,48] Sleep duration was assessed based on a single question "About how many hours sleep do you get in every 24 hours (please include naps)?" Detailed descriptions of each covariate are presented in ESI Table S5.†

2.5 Statistical analysis

Baseline characteristics were expressed as numbers (percentages) for categorical variables or as median (interquartile range [IQR]) values for continuous variables stratified by the MEDAS continuous score in tertiles. Continuous variables were filled with the median, while categorical variables were imputed using either the largest group (missing rate <3%) or the missing indicator method (missing rate ≥ 3%). Information on missing rates is shown in ESI Table S5.†

Participants were categorized into tertiles according to MedDiet adherence. Two multivariable Cox proportional hazard regression models were constructed to investigate associations between MedDiet adherence and CP risk: the minimally adjusted model was adjusted for age, sex, and total energy intake; the fully adjusted model included additional adjustments for ethnicity, TDI, education, smoking status, and physical activity, and was treated as the main model. The proportional hazard assumption was tested and verified using Schoenfeld residual methods (all $p > 0.05$). Results are pre-

sented as hazard ratios (HRs) with 95% confidence intervals (CIs). The duration of follow-up was calculated as the interval between the latest eligible dietary report and the first CP diagnosis, death, loss to follow-up, or end of follow-up (*i.e.*, 31 October 2022 for England, 31 August 2022 for Scotland, and 31 May 2022 for Wales), whichever came first.

To evaluate the potential effects of related covariates, we conducted subgroup analyses stratifying participants by sex, age (<60 and ≥60 years), education (below college/college and above), TDI (low, moderate, high deprivation), and physical activity (low, moderate, high intensity), and calculated the interaction *p* value accordingly. However, since less than 30% of pancreatitis cases were classified into subtypes of CP,[40] we were unable to separately examine the associations between MedDiet adherence and the risks of alcohol-induced chronic pancreatitis *versus* other chronic pancreatitis.

A series of sensitivity analyses was conducted to test the robustness of our findings: (1) we assessed the MedDiet adherence by the standard MEDAS continuous and MEDAS binary score. Instead of modifying the wine category, we followed the conventional calculation by treating ≥7 servings of wine per week as the cut-off. (2) We employed the Alternate Mediterranean Diet score (AMED) to represent MedDiet adherence, based on the methods described by Trichopoulou *et al.* The AMED encompassed 9 food/nutrient groups including vegetables, legumes, fruits and nuts, cereals, fish and seafood, monounsaturated fats to saturated fats ratio, dairy products, meat and meat products, and alcohol.[43,49] Participants with intakes above the sex-specific median were given 1 point, and those with all other intakes were given 0 points. For alcohol consumption, 1 point was assigned to men who consumed between 10 to 25 grams per day, and to women who consumed between 5 and 15 grams per day.[50] Details of the scoring methods are provided in ESI Table S3.† (3) We repeated the analyses with additional adjustments for potential confounders, including BMI, CCI, sleep duration, and baseline diabetes. (4) Multiple imputation by chained equations was used to impute missing values of covariates.[51] (5) The analysis further excluded participants who developed CP within 3, 4, and 5 years of follow-up. (6) The analysis was further limited to participants who completed at least two 24-hour diet recalls with typical dietary intake to ensure a more stringent measure.

In addition, the potential mediating effects of inflammation (measured by C-reactive protein) and metabolic status in the CP outcome were investigated by carrying out exploratory mediation analyses. Metabolic status was measured by four criteria involving high triglycerides, elevated blood pressure, high fasting glucose, and low HDL-cholesterol, with participants meeting fewer than two criteria considered metabolically healthy.[52] To be specific, the mediation model was constructed with individual regression paths to assess the following associations, as illustrated in Fig. 3A: (1) the total effect between exposure (MEDAS continuous score) and outcome (incident CP); (2) the 'a' path: between MEDAS continuous score and the mediators (C-reactive protein, metabolic status); (3) the 'b' path: between the mediators and incident CP,

adjusted for MEDAS continuous score. The indirect effect was calculated as the product of the 'a' and 'b' paths, and the proportion mediated was determined by dividing the indirect effect by the total effect. Quasi-Bayesian confidence intervals for the estimated effects were obtained through 1000 simulations by using a mediation package in R.[53]

All analyses were conducted using R (Version 4.2.1), with a two-tailed *p* value < 0.05 considered significant.

3. Results

3.1 Baseline characters

Baseline characters of the study population, stratified by level of MedDiet adherence (low, medium, and high MEDAS continuous scores), are shown in Table 1. The majority of participants were of white ethnicity with a median age of 60.0 years. During a mean (SD) follow-up of 10.8 (1.6) years of the 190 790 participants included, there were 214 cases of incident CP. Participants with higher MEDAS continuous scores were more likely to be female, have a lower BMI, higher education level, higher physical activity intensity, lower total energy intake, and were more likely to have never smoked, as well as having lower rates of baseline diabetes.

3.2 Mediterranean diet adherence and the risk of incident chronic pancreatitis

After multivariable adjustment, inverse associations between adherence to the MedDiet and the risk for CP were observed (Table 2 and ESI Fig. S1,† HR per standard deviation (SD) increase in MEDAS continuous score: 0.82; 95% CI: 0.72–0.95; *p* = 0.006). When divided into tertiles, a higher MedDiet adherence as defined by the MEDAS continuous score was linearly associated with reduced CP risk (*p*-trend = 0.003). Compared to participants in the lowest tertiles, high (HR: 0.57; 95% CI: 0.40–0.82; *p* = 0.002) but not moderate (HR: 0.83; 95% CI: 0.61–1.13; *p* = 0.243) adherence was associated with lower CP risk.

In subgroup analyses, the main findings remain consistent after stratification by age, education level, smoking status, TDI, and physical activity. We observed no statistically significant interaction with these variables (Fig. 2). In the analysis where components were sequentially removed from the total score, the association remained consistently stable (ESI Table S7†). In the analysis examining the associations between individual dietary components of MEDAS and incident CP, the only individual components predictive of CP incidence were the intake of olive oil, sweetened or carbonated drinks, and butter, margarine or cream; associations between other individual components and CP incidence were nonsignificant (ESI Table S8†).

3.3 Sensitivity analyses and mediation analyses

The results remained robust to a range of sensitivity analyses (ESI Tables S9–S12†). Specifically, in analyses where adherence to the Mediterranean diet was evaluated using the standard MEDAS continuous or MEDAS binary score, the results showed

Table 1 Baseline characteristics across tertiles of the MEDAS continuous score (n = 190 790)

	Overall (N = 190 790)	Low (>0–5.3) (N = 63 597)	Middle (≥5.3–6.7) (N = 63 596)	High (≥6.7) (N = 63 597)	p^a
Age, year	60.0 [53.0, 65.0]	59.0 [52.0, 65.0]	60.0 [53.0, 66.0]	61.0 [54.0, 66.0]	<0.001
Female (%)	104 958 (55.0)	29 372 (46.2)	35 397 (55.7)	40 189 (63.2)	<0.001
White (%)	183 059 (95.9)	61 376 (96.5)	61 179 (96.2)	60 504 (95.1)	<0.001
Townsend deprivation index (%)					<0.001
Low deprivation	63 614 (33.3)	20 697 (32.5)	21 684 (34.1)	21 233 (33.4)	
Moderate deprivation	63 580 (33.3)	21 231 (33.4)	21 459 (33.7)	20 890 (32.8)	
High deprivation	63 596 (33.3)	21 669 (34.1)	20 453 (32.2)	21 474 (33.8)	
College and above (%)	81 039 (42.5)	22 596 (35.5)	27 554 (43.3)	30 889 (48.6)	<0.001
Smoking status (%)					
Never	108 495 (56.9)	34 597 (54.4)	36 451 (57.3)	37 447 (58.9)	<0.001
Previous	67 731 (35.5)	22 558 (35.5)	22 576 (35.5)	22 597 (35.5)	
Current	14 564 (7.6)	6442 (10.1)	4569 (7.2)	3553 (5.6)	
Physical activity (%)					
Low intensity	29 492 (15.5)	11 599 (18.2)	9683 (15.2)	8210 (12.9)	<0.001
Moderate intensity	68 488 (35.9)	22 466 (35.3)	23 104 (36.3)	22 918 (36.0)	
High intensity	63 860 (33.5)	19 203 (30.2)	20 967 (33.0)	23 690 (37.3)	
Unknown	28 950 (15.2)	10 329 (16.2)	9842 (15.5)	8779 (13.8)	
Body mass index (%)					<0.001
<25 kg m^{-2}	71 848 (37.7)	20 204 (31.8)	24 208 (38.1)	27 436 (43.1)	
25–29.9 kg m^{-2}	79 383 (41.6)	27 641 (43.5)	26 662 (41.9)	25 080 (39.4)	
>30 kg m^{-2}	39 559 (20.7)	15 752 (24.8)	12 726 (20.0)	11 081 (17.4)	
Charlson comorbidity index	0.0 [0.0, 0.0]	0.0 [0.0, 0.0]	0.0 [0.0, 0.0]	0.0 [0.0, 0.0]	<0.001
Charlson comorbidity index = 0 (%)	167 653 (87.9)	55 433 (87.2)	56 075 (88.2)	56 145 (88.3)	<0.001
Sleep duration, hour	7.0 [7.0, 8.0]	7.0 [6.7, 8.0]	7.0 [7.0, 8.0]	7.0 [7.0, 8.0]	<0.001
Total energy intake, kcal d^{-1}	1976.9 [1651.5, 2347.4]	1985.1 [1641.7, 2371.8]	1967.4 [1646.8, 2329.0]	1978.7 [1664.4, 2340.7]	<0.001
Baseline diabetes (%)	8287 (4.3)	3260 (5.1)	2688 (4.2)	2339 (3.7)	<0.001
C-reactive protein, mg L^{-1}	1.2 [0.6, 2.4]	1.3 [0.7, 2.7]	1.2 [0.6, 2.4]	1.1 [0.5, 2.2]	<0.001
Metabolic status (%)					
Healthy	93 652 (49.1)	28 837 (45.3)	31 303 (49.2)	33 512 (52.7)	<0.001
Unhealthy	70 765 (37.1)	26 026 (40.9)	23 540 (37.0)	21 199 (33.3)	
Unknown	26 373 (13.8)	8734 (13.7)	8753 (13.8)	8886 (14.0)	

Abbreviations: MEDAS, Mediterranean Diet Adherence Screener (score). ^{a} p values were calculated by χ^2 tests or Kruskal–Wallis tests.

Table 2 Associations between Mediterranean diet adherence and risk of chronic pancreatitis (n = 190 790)

	Cases/person-years	Minimally adjusted model^a		Fully adjusted model^b	
		HR (95%CI)	p	HR (95%CI)	p
Per SD		**0.79 [0.69, 0.90]**	**0.001**	**0.82 [0.72, 0.95]**	**0.006**
Low	96/693 229	1 (reference)		1 (reference)	
Moderate	72/687 582	0.78 [0.58, 1.06]	0.119	0.83 [0.61, 1.13]	0.243
High	46/684 658	**0.53 [0.37, 0.75]**	**<0.001**	**0.57 [0.40, 0.82]**	**0.002**
p-Trend			**<0.001**		**0.003**

Abbreviations: MEDAS, Mediterranean Diet Adherence Screener (score); HR, hazard ratio; CI, confidence interval, SD, standard deviation. ^{a} Minimally adjusted model adjusted for age, sex, and total energy intake. ^{b} Fully adjusted model additionally adjusted for ethnicity, education, Townsend deprivation index, smoking status, and physical activity.

slight attenuation but remained largely consistent (MEDAS continuous, HR high *vs.* low: 0.66; 95% CI: 0.47–0.93; p = 0.018; MEDAS binary, HR high *vs.* low: 0.68; 95% CI: 0.49–0.96; p = 0.028). However, when we used the AMED to represent MedDiet adherence, the result showed a similar effect size but was not statistically significant (p = 0.095). Compared to participants with low MedDiet adherence, those with high adherence were at reduced CP risk when further adjusted for BMI (HR: 0.58; 95% CI: 0.41–0.83; p-trend = 0.003), CCI (HR: 0.58; 95% CI: 0.40–0.83; p-trend = 0.003), sleep duration (HR: 0.57; 95% CI: 0.40–0.82; p-trend = 0.003), baseline 2 diabetes

(HR: 0.58; 95% CI: 0.41–0.84; p-trend = 0.004) or using the multiple imputation method (HR: 0.57; 95% CI: 0.40–0.81; p-trend = 0.002). Results were similar when we repeated analyses excluding participants who developed CP within 3, 4, and 5 years of follow-up (Table S10†). When restricting the analysis to participants with a minimum of two typical dietary reports, the result indicated that the significant inverse associations became even more pronounced (ESI Table S11 and Fig. S2,† HR high *vs.* low: 0.49; 95% CI: 0.29–0.82; p = 0.006).

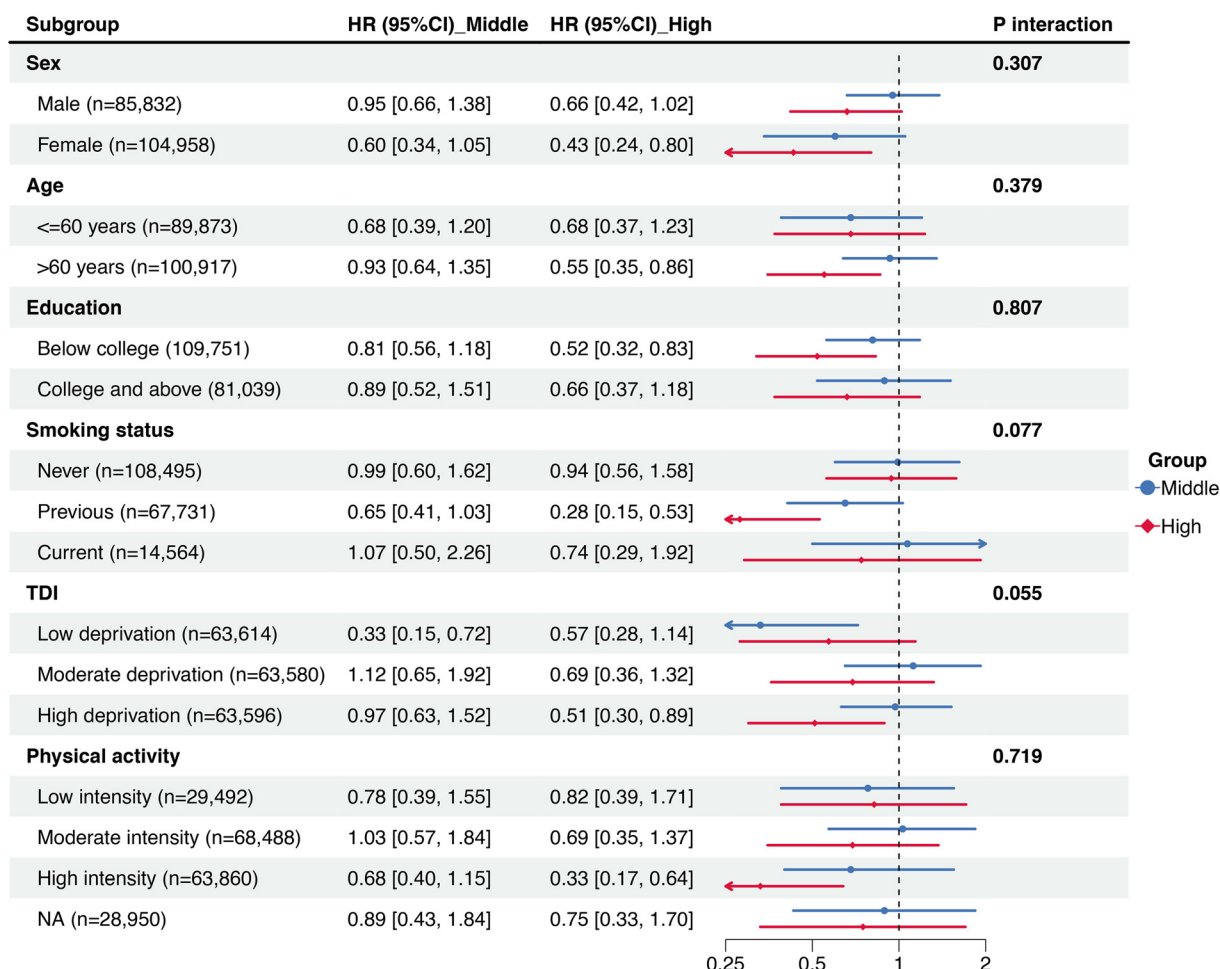In the mediation analyses, we found that metabolic status mediated 4.74% of the association between MedDiet adher-

Subgroup	HR (95%CI)_Middle	HR (95%CI)_High	P interaction
Sex			0.307
Male (n=85,832)	0.95 [0.66, 1.38]	0.66 [0.42, 1.02]	
Female (n=104,958)	0.60 [0.34, 1.05]	0.43 [0.24, 0.80]	
Age			0.379
<=60 years (n=89,873)	0.68 [0.39, 1.20]	0.68 [0.37, 1.23]	
>60 years (n=100,917)	0.93 [0.64, 1.35]	0.55 [0.35, 0.86]	
Education			0.807
Below college (109,751)	0.81 [0.56, 1.18]	0.52 [0.32, 0.83]	
College and above (81,039)	0.89 [0.52, 1.51]	0.66 [0.37, 1.18]	
Smoking status			0.077
Never (n=108,495)	0.99 [0.60, 1.62]	0.94 [0.56, 1.58]	
Previous (n=67,731)	0.65 [0.41, 1.03]	0.28 [0.15, 0.53]	
Current (n=14,564)	1.07 [0.50, 2.26]	0.74 [0.29, 1.92]	
TDI			0.055
Low deprivation (n=63,614)	0.33 [0.15, 0.72]	0.57 [0.28, 1.14]	
Moderate deprivation (n=63,580)	1.12 [0.65, 1.92]	0.69 [0.36, 1.32]	
High deprivation (n=63,596)	0.97 [0.63, 1.52]	0.51 [0.30, 0.89]	
Physical activity			0.719
Low intensity (n=29,492)	0.78 [0.39, 1.55]	0.82 [0.39, 1.71]	
Moderate intensity (n=68,488)	1.03 [0.57, 1.84]	0.69 [0.35, 1.37]	
High intensity (n=63,860)	0.68 [0.40, 1.15]	0.33 [0.17, 0.64]	
NA (n=28,950)	0.89 [0.43, 1.84]	0.75 [0.33, 1.70]	

Group: Middle, High

Scale: 0.25 0.5 1 2

Fig. 2 Subgroup analyses of the associations between Mediterranean diet adherence and the risk of chronic pancreatitis stratified by covariates. The reference group in each subgroup was the lowest tertile of the MEDAS continuous score. HR (95% CI)_middle (shown in blue) and HR (95% CI)_high (shown in red) represent the hazard ratios and their corresponding confidence intervals for the middle and high tertiles of the MEDAS continuous score, respectively. Abbreviations: CI, confidence interval; HR, hazard ratio; NA, not available; TDI, Townsend deprivation index.

ence defined by the MEDAS continuous score and the incidence of CP, while the mediating role of C-reactive protein was not significant (Fig. 3 and ESI Table S12†).

4. Discussion

To the best of our knowledge, this is the first longitudinal cohort study to investigate the association between a whole dietary pattern (i.e. the Mediterranean diet) and the risk of CP. Based on data from a large-scale cohort of 190 790 middle-aged adults, we observed a significant inverse association between adherence to MedDiet and the risk of CP. Compared to participants in the lowest tertiles, individuals with the highest adherence to MedDiet were associated with a 43% reduced risk of developing CP. The association is stable when assessing MedDiet adherence by different nutritional measurement tools, including both adapted and conventional MEDAS continuous score, as well as the conventional MEDAS score. However, no statistically significant results were observed

when adherence to MedDiet was measured by AMED. This may be due to healthy volunteer bias in the UK Biobank cohort.[54] Unlike MEDAS, which assigns points based on the predefined cut-off values, the scoring of AMED is based on whether intakes are above or below the sex-specific median of the study subjects. Due to participants' better health, these medians might be higher than typical, causing misclassification of individuals with relatively high adherence, thereby weakening the observed association. In this case, the MEDAS score may be more practical for this study as it used predefined cut-off values based on dietary guidelines rather than cohort-specific medians.

Previous investigations into the relationship between dietary intake and CP have been limited, mainly involving cross-sectional studies that primarily examine single foods and nutrients.[8–12,14] However, these studies do not address the broader role of overall dietary patterns, missing the complex interactions between dietary components. Recently, there has been a limited number of studies exploring the role of overall dietary patterns in relation to chronic pan-
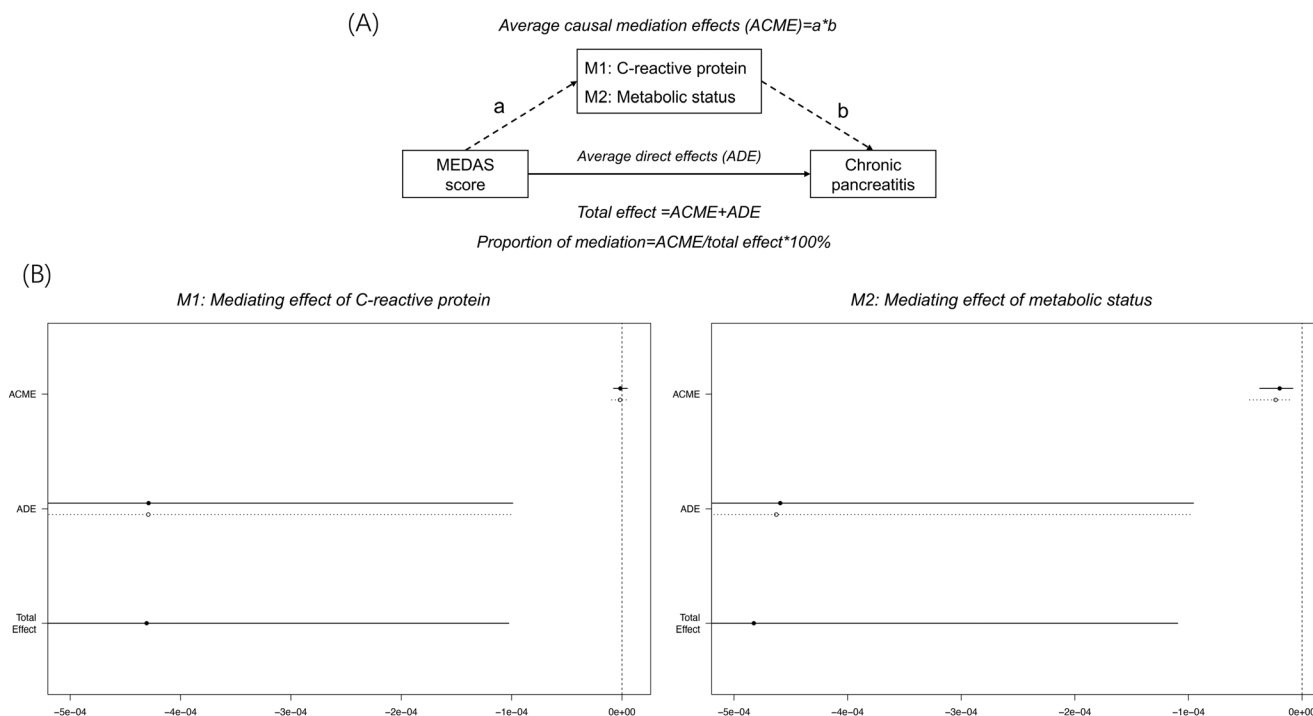
Fig. 3 The schematic diagram (A) and mediation effects (B) of inflammation and metabolic status between the Mediterranean diet adherence defined by the MEDAS continuous score and risk of chronic pancreatitis. The x-axis shows the mediation effect estimates, and the y-axis shows three different effects (the mediating effect, the direct effect, and the total effect). ACME, average causal mediation effects; ADE, average direct effect. The mediation effects of the mediators (M1: C-reactive protein, and M2: metabolic status) were individually examined in separate structural equation models.

creatitis. In particular, a recent cross-sectional, case-control study[13] comparing individuals with CP (n = 52) to healthy controls (n = 48) showed that those with CP exhibited lower overall dietary quality compared to controls. In this study, dietary quality was assessed by two separate nutritional measurement tools: the Healthy Eating Index and the Mediterranean diet score. In addition, a decreased consumption of vegetables was observed in the CP group in comparison to controls. In another cross-sectional study involving 66 patients with CP and 94 control subjects,[15] deviations in food and nutrient intake were also observed in the patient groups compared to healthy controls. While this study did not find significant differences in diet quality, it did observe changes in food group consumption in individuals with CP, including decreased consumption of coffee, fruits and vegetables, whole grain products, nuts, and alcoholic beverages, and increased intake of butter and margarine, high-fat sausages, boiled potatoes, and white bread. However, since both studies focused mainly on the nutritional status of CP patients and measured nutritional status after disease onset, the result may have been influenced by disease-related metabolic degenerations, which are contributing factors linked to low diet quality. Despite the continuous implication of diet in the pathology of CP, the existing data do not offer a clear picture, particularly regarding the impact of overall dietary patterns. Our study with a prospective cohort design filled this gap and provided strong

evidence to support the association between a healthy dietary pattern and reduced CP risk.

Regarding the potential mechanisms, our mediation analysis found that the mediating effect of inflammation in the CP outcome is not statistically significant, whereas the mediating role of metabolic status was observed. The lack of a significant mediating effect of inflammation may be due to the following reasons: first, inflammation may not contribute to the etiology of CP since it is not considered one of its established risk factors;[55] and second, C-reactive protein may not fully represent an individual's inflammation status, and since it can fluctuate, baseline C-reactive protein levels may not accurately reflect one's true inflammation status. The Mediterranean diet minimizes the consumption of meat, milk, and butter, which are high in saturated fat, and emphasizes healthy fats from sources like olive oil, nuts, and whole grains, resulting in a lipid-lowering effect.[56] A prospective cohort study has shown that increased intrapancreatic fat deposition is linked to a higher risk of all pancreatic diseases, including CP.[57] In addition, abundant in insoluble fiber, MedDiet significantly influences gut microbiota composition and activity, leading to the production of metabolites that regulate immune responses and various metabolic pathways.[56] These dietary effects on the microbiota and immune system might have downstream effects on CP.[58] In the mediation analyses, we provided evidence for the mediating role of metabolic status, which accounted for 4.74% of the effect. Furthermore, lipoprotein

disorder and increased oxidative stress have been implicated in the pathogenesis of CP.[59,60] Mediterranean diet is abundant in antioxidant vitamins, natural folate, phytochemicals, and minerals. Adequate intake of dietary antioxidants within the MedDiet reduces oxidative lipid damage[61] and may potentially lower the risk of CP.

The strengths of this study lie in its large prospective cohort, the long follow-up period, objective case ascertainment *via* linkage to population-based registers, and robust results from a wide range of sensitive analyses, including multiple methods for assessing MedDiet adherence. However, there are also several limitations. First, despite efforts to minimize possible biases from reverse causation and residual confounding by excluding participants who developed CP within the first two-year follow-up and adjusting for essential confounders, causality cannot be inferred due to the observational nature of this study. To validate our findings, intervention studies like randomized controlled trials are warranted. Another limitation is that our cohort is predominantly Caucasian, which may not accurately represent the general population. Nevertheless, as previously reported, the UK Biobank's large size and diverse exposure metrics allow for valid assessment of exposure–disease relationships that are applicable to broader populations.[54] Furthermore, the assessment of dietary intake presents challenges and may introduce specific limitations to our research. We utilized dietary data from the Oxford WebQ, a self-administered questionnaire. This method may introduce measurement error. In addition, dietary habits may change during this long follow-up. However, a recent study validated the accuracy of the Oxford WebQ dietary questionnaire, especially when averaging multiple measures, indicating it has comparable validity to interviewer-based recall methods.[29] Another research, involving around 20 000 UK Biobank participants who completed a touchscreen dietary assessment questionnaire, revealed moderate to substantial agreement in the responses between the baseline assessment and a follow-up approximately 4.4 years later.[30] These findings suggest that the dietary intake estimates provided by the UK Biobank are indicative of habitual intake.

Among the risk factors identified in current guidelines and the M-ANNHEIM system, only alcohol consumption, nicotine consumption, and nutritional factors are modifiable. Our findings highlight the importance of public health professionals taking proactive measures, as our study suggests that the MedDiet, associated with improvements in metabolic health, may be recommended as a preventive measure for individuals with established risk factors or a history of acute pancreatitis. Further studies are warranted to validate our findings.

5. Conclusions

In conclusion, our results based on a large prospective cohort support the inverse association between higher adherence to the Mediterranean diet and reduced risk of developing chronic pancreatitis. This finding highlights the importance of a healthy dietary pattern for chronic pancreatitis prevention.

Ethical considerations

Ethical approval for the UK Biobank was granted by the North West-Haydock Research Ethics Committee (REC reference: 21/NW/0157). Written informed consent has been obtained from the patients to publish this study.

Author contributions

Chunhua Zhou: conceptualization (lead); methodology (supporting); writing – original draft (equal). Jiawei Geng: formal analysis (lead); visualization (equal); writing – review and editing (supporting). Hanyi Huang: writing – original draft (equal); visualization (equal). Lintao Dan: formal analysis (supporting); writing – review and editing (supporting). Zhipeng Wu: methodology (supporting). Xixian Ruan: formal analysis (supporting). Yao Zhang: conceptualization (supporting); writing – review and editing (supporting). Jie Chen: conceptualization (equal); data curation (lead); supervision (lead); writing – review and editing (equal). Jing Sun: conceptualization (equal); methodology (equal). Duowu Zou: methodology (equal); funding acquisition (lead); writing – review and editing (equal); project administration (lead).

Data availability

Researchers can require the data and approval from the UK Biobank (**https://www.ukbiobank.ac.uk**).

Conflicts of interest

All authors declare that they have no conflict of interest.

Acknowledgements

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