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## Association between meat consumption and incident acute pancreatitis: a prospective cohort study†

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**Background:** Previous studies indicated the potential role of consumption of different types of meat in the etiology of acute pancreatitis (AP), but no clear link has been established. This study aimed to investigate the association between consumption of 4 types of meat (processed meat, unprocessed red meat, poultry, and fish) and the risk of incident AP. **Materials and methods:** We included 489 708 participants from the UK Biobank between 2006 and 2010. A food frequency questionnaire (FFQ) was used to document the frequency of four types of meat. Data from validated 24-hour dietary recalls were used to quantify the meat intake and reduce measurement errors. The outcomes of our study were incident AP among participants. Hazard ratios (HRs) with 95% confidence intervals (CIs) for the associations between meat consumption and incident AP were calculated using Cox proportional hazard models. **Results:** Over a mean (standard deviation) follow-up of 13.2 (2.1) years, 3079 incident AP cases were recorded. We observed that higher consumption of processed meat was associated with a higher risk of incident AP (per 25 g per d: HR: 1.29, 95% CI: 1.12–1.47). In contrast, higher consumption of fish intake was associated with a lower risk of AP (per 25 g per d: HR: 0.78, 95% CI: 0.68–0.89). Replacing one, two, and three servings per week of processed meat with fish per week was associated with a 6% (95% CI: 2%–9%), 11% (95% CI: 4%–17%), and 16% (95% CI: 6%–24%) reduced risk of incident AP. **Conclusion:** More frequent processed meat consumption was associated with an elevated risk of incident AP, while more frequent fish consumption was associated with a lower risk of incident AP. Our study found that a diet that substitutes fish for processed meat may mitigate the risk of incident AP.

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### 1. Introduction

Acute pancreatitis (AP), an inflammatory disorder of the pancreas, is the predominant cause of hospital admission for gas-

trointestinal disorders in many countries.<sup>1</sup> AP predominantly affects middle-aged and older adults, with a median age of 58 years (interquartile range 45–74 years) reported in European patients.<sup>2</sup> The incidence of AP has increased from 21.4 to 48.2 per 100 000 persons over the past 20 years.<sup>3</sup> Although there have been substantial improvements in the clinical management of AP, it is reported that about 20% of AP patients are at risk of developing necrosis of pancreatic or organ failure.<sup>4</sup> Therefore, it is critical to identify modifiable risk factors and develop preventive strategies against AP.

Recent studies have shed more light on the relationship between diet and acute pancreatitis. Oskarsson *et al.* (2013) found a significant inverse association between vegetable consumption and the risk of non-gallstone-related acute pancreatitis in a population-based prospective cohort study, suggesting that vegetables may have a protective effect.<sup>5</sup> Another study by Oskarsson *et al.* (2014) revealed that high dietary glycemic load is linked to an increased risk of non-gallstone-related acute pancreatitis, indicating the potential impact of glycemic factors on pancreatitis risk.<sup>6</sup>

The pathogenesis of AP involves an obstruction in pancreatic secretion pathways that hinders the release of zymogen

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granules containing digestive enzymes.<sup>1</sup> This leads to premature activation of these enzymes, and subsequent autodigestion of the pancreas.<sup>7</sup> Studies have revealed that dietary constituents affected the secretion pattern of the pancreas.<sup>8–10</sup> A previous review had suggested the possible role of diet in the etiology of AP, but no clear link has been established.<sup>11</sup>

As a major diet constituent, meat was one of the major dietary sources of protein, fat, and cholesterol intake,<sup>12</sup> which have been associated with the onset of AP.<sup>13,14</sup> Mao *et al.* (2023) used a two-sample Mendelian randomization study to explore the causal relationships between dietary habits and pancreatitis, and found that fruit intake may be protective against pancreatitis, while processed meat consumption has potential adverse impacts.<sup>15</sup> Meanwhile, other studies hinted that red and processed meat are major dietary sources of *N*-nitroso compounds (NOCs), heterocyclic amines (HCAs), and polycyclic aromatic hydrocarbons (PAHs), which are risk factors of pancreatic cancer.<sup>16–18</sup> A few studies have revealed the association between red and processed meat consumption and an increased risk of incident acute pancreatitis,<sup>11,14</sup> while the impact of other types of meat on AP is still unknown.<sup>19</sup>

Hence, we conducted a large-population prospective cohort study based on the UK Biobank to investigate the association between the consumption of processed meat, unprocessed red meat, poultry, and fish and the risk of incident acute pancreatitis.

## 2. Materials and methods

### 2.1 Study population

The current analysis leveraged data from the UK Biobank, a large-scale cohort project that recruited over 500 000 participants aged 40–69 years from 2006 to 2010 across the United Kingdom.<sup>20</sup> Participants attended one of the twenty-two assessment centers across England, Wales, and Scotland,<sup>21</sup> where they signed an electronic consent and completed a touchscreen questionnaire, a verbal interview, a physical measurement, and biological sample collection.<sup>21</sup> The overall ethical approval for the UK Biobank (REC reference: 21/NW/0157) was provided by the North West-Haydock Research Ethics Committee, U.K.

After the initial recruitment, we excluded participants who had missing data on meat intake ( $N = 11\,157$ ) or history of AP ( $N = 1596$ ). Finally, we recruited 489 708 participants in the primary analysis (Fig. 1).

### 2.2 Meat consumption measures

A validated food frequency questionnaire (FFQ) was administered at the baseline (2006–2010), which comprises 47 dietary items. The exposure was consumption of different types of meat: (1) processed meat containing bacon, ham, sausages, meat pies, kebabs, burgers, and chicken nuggets; (2) unprocessed red meat containing unprocessed beef, lamb/mutton, and unprocessed pork; (3) unprocessed poultry; and (4) unprocessed fish, containing oily and non-oily fish. Participants were asked about their frequency of consumption of each meat item, with eight options to select: ‘never’, ‘less than once a

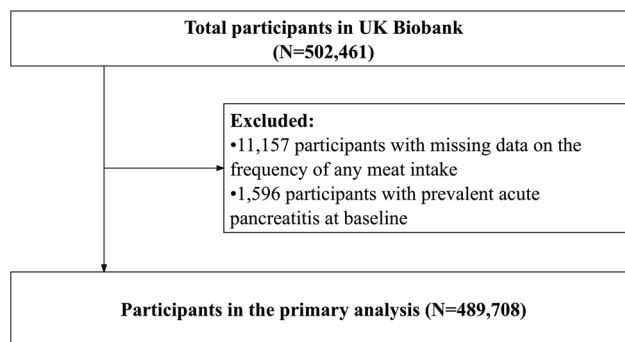


Fig. 1 Inclusion of the study sample and study design.

week’, ‘once a week’, ‘2–4 times a week’, ‘5–6 times a week’, ‘once or more daily’, ‘do not know’, ‘prefer not to answer’. Answers on meat consumption have been changed into 0, 0.5, 1, 3, 5.5, and 7 times per week. Those who had a response of ‘do not know’ or ‘prefer not to answer’ were converted into missing values, and participants with missing data on meat consumption were removed from the analysis. Meat consumption was further categorized as follows: (1) 0 times per week, (2) 0.1–0.9 times per week, (3) 1–1.9 times per week, (4) 2–4 times per week, and (5) >4 times per week.

As a complement to reducing measurement error bias,<sup>22</sup> we used data from the 24-hour dietary recall to estimate the mean meat intake as suggested by previous studies.<sup>23–25</sup> Participants were invited to complete the Oxford WebQ questionnaire on up to five occasions (April 2009–September 2010, February 2011–April 2011, June 2011–August 2011, October 2011–December 2011, and April 2012–June 2012).<sup>26</sup> Among the 210 962 participants with available 24-hour dietary recalls, we further excluded (1) 107 394 participants reporting only one typical dietary intake and (2) 1856 participants with no records of plausible energy intake (defined as <800 or >4200 kcal per day for males, <600 or >3500 kcal per day for females).<sup>27</sup> Finally, we included 101 712 participants to calculate the mean weight of different types of meat. The food intake weight of each food (grams) was calculated by multiplying the number of portions with the standard portion size specified in the standard United Kingdom food composition tables.<sup>22</sup> The mean intake of meat for each specific category (*e.g.*, 0–0.9 times per week) was then calculated across all records of Oxford WebQ questionnaires and subsequently assigned to participants within the corresponding category.

### 2.3 Outcome ascertainment

The outcomes were incident AP among participants, ascertained *via* data linkage to primary health care, hospital inpatient admissions, and death records. Individuals with incident AP were identified in hospital inpatient data using the International Classification of Disease Tenth Revision (ICD-10) codes K85.0–3, K85.8, and K85.9, and in primary care data using specific codes mapping to ICD-10. History of AP was determined as AP cases before recruitment at the baseline.



## 2.4 Covariate assessment

In our study, variables were chosen as potential confounding factors according to prior knowledge of associated factors and previous studies,<sup>14,28</sup> including the modified healthy eating index (a measurement of healthy diet derived from baseline FFQ records of food items including fruits, vegetables, whole grains and refined grains, with details of calculation described elsewhere<sup>29</sup>), alcohol drinking (less than once per week, once or twice per week, three or four times per week, and daily or almost daily), oil intake (use or never/rarely use spread made with oil), dairy product (cheese) intake ( $\geq 2$  or  $< 2$  servings per day), Charlson comorbidity index, sociodemographic factors (age at the baseline, ethnicity, Townsend Deprivation Index [TDI], and education), baseline gallstone, cholecystectomy status (ascertained *via* data linkage to primary health care, hospital inpatient admissions, and self-report) and blood triglyceride (TG) level (continuous) and lifestyle factors (body mass index [BMI], physical activity level, smoking status and sleep duration). Education levels were categorized into two groups (with or without a university/college degree). TDI is a measure of socioeconomic deprivation.<sup>30</sup> Physical activity was calculated and categorized into three levels: low, moderate, and high, according to the official guidelines for data processing and analysis of the International Physical Activity Questionnaire Short Form.<sup>31</sup> Sleep duration was categorized as  $< 7$ , 7–8, or  $> 8$  hours per day, with  $< 7$  and  $> 8$  hours considered unhealthy<sup>32</sup> and analyzed as a categorical variable.

## 2.5 Statistical analyses

Baseline characteristics were collected for all participants and stratified by whether AP occurred during follow-up. Continuous variables were summarized in mean (standard deviation [SD]) and categorical variables in number (percentage). We calculated the follow-up survival time (person-year) from the date of dietary assessment to the date of AP diagnosis, date of loss, or the end of follow-up (October 31, 2022) or date of death, whichever came first.

In the primary analyses, we constructed two Cox proportional hazards models to evaluate the hazard ratios (HRs) and 95% confidence intervals (CIs): (1) the minimally adjusted model adjusted for age, sex, and ethnicity and (2) the fully adjusted model was further adjusted for TDI, education level, physical activity level, smoking status, alcohol drinking status, BMI, and the modified HEI score.

The linear *P* trend across the categories of meat consumption was calculated by imputing median values to the corresponding categories. We also quantified the effect of meat intake of 25 g d<sup>-1</sup> based on mean intake from 24-hour dietary recalls within each intake category among the total study samples.

Aside from the primary analyses above, we furthermore conducted two secondary analyses: (1) evaluating the associations between specific subtypes of unprocessed red meat (beef mutton and pork) and fish (oily and non-oily) and the risk of incident AP, and (2) to investigate the effect of substituting (a)

processed meat or (b) unprocessed red meat with fish per one serving on AP risk, we used two leave-one-out models for substitution analyses,<sup>33–35</sup> which consisted of the exposure (fish consumption), other types of meat without the substituting component (processed meat or unprocessed red meat), total intake of meat and the covariates in the fully adjusted model:

$$\begin{aligned} \log(h(t; x)) = & \log(h_0(t)) + \hat{\beta}_1 \text{ fish} \\ & + \hat{\beta}_2 \text{ unprocessed red meat} + \hat{\beta}_3 \text{ poultry} \\ & + \hat{\beta}_4 \text{ total intake of meat} + \hat{\beta}_5 \text{ covariates} \end{aligned} \quad (\text{a})$$

$$\begin{aligned} \log(h(t; x)) = & \log(h_0(t)) + \hat{\beta}_1 \text{ fish} \\ & + \hat{\beta}_2 \text{ processed meat} + \hat{\beta}_3 \text{ poultry} \\ & + \hat{\beta}_4 \text{ total intake of meat} + \hat{\beta}_5 \text{ covariates.} \end{aligned} \quad (\text{b})$$

The exponential of fish consumption ( $\hat{\beta}_1$ ) directly estimates the substituting effect of replacing the same serving per week of processed meat or unprocessed red meat with fish intake, while keeping total meat consumption unchanged.

To further assess the discrepancies in major subgroups, subgroup analyses were performed, and multiplicative interactions were assessed in the participants stratified by sex, age, smoking status, education, physical activity, and drinking status. Moreover, a series of sensitivity analyses were conducted to test the robustness of our results. On the basis of the fully adjusted model, we further: (1) adjusted for CCI, sleep duration ( $< 7$ , 7–8,  $> 8$  hours per day) and frequency of alcohol consumption instead of alcohol drinking status; (2) adjusted for dairy intake and use of spread made with butter and other oils; (3) further performed baseline cholecystectomy and gallstone status and blood triglyceride level analyses; (4) examined the association in the mutually adjusted model (including all four types of meat); (5) treated TDI, BMI and sleep duration as continuous variables; (6) excluded incident acute pancreatitis cases that occurred in the first one, two, and three years of follow-up to reduce the possibility of reverse causality; (7) re-categorized the meat consumption by including no consumption, and used '0.1–0.9 times per week' as the referent category, given the zero intake group may have negative health effects due to protein deficiency; (8) reprocessed the covariates with multiple imputations; and (9) reconstructed an age-scaled Cox regression model to further control the potential confounding effect of age at the baseline.<sup>36</sup>

We additionally performed a mediation analysis to quantify the contribution of baseline blood triglyceride levels in the associations between the pre-defined four types of meat and AP risk. Specifically, the direct effect of meat intake was separated apart from the total effect, which included the indirect effect of blood triglyceride levels. The proportion of the meat–AP associations mediated by blood triglyceride levels was calculated as indirect effect/total effect. Quasi-Bayesian confidence intervals were calculated through bootstrap with 1000 stimulations. The mediating analysis was conducted using the 'mediation' package in R.



All analyses were executed using R software (version 4.3.2), with details of every R package listed in Table S15.† A two-sided *P*-value <0.05 was considered as statistically significant.

### 3. Results

#### 3.1 Baseline characteristics

Baseline characteristics of the participants are displayed in Table 1. In our study, 489 708 participants were

recruited and followed for a mean (SD) of 13.6 (2.1) years. Among the gathered samples, the mean (SD) age was 57.0 (8.1) years, and 267 189 (54.6%) were females, in the duration of follow-up, 3079 cases of incident AP were documented. In comparison with participants who did not develop incident AP, those who did are more likely to be lowly educated and physically inactive, as well as to have a history of smoking and drinking, along with higher TDI, BMI, CCI, and lower sleep duration (all *P*-values <0.001).

**Table 1** Baseline characteristics of the participants included in the primary analysis

Characteristics	Overall ( <i>N</i> = 489 708)	Incident acute pancreatitis ( <i>N</i> = 3079)	Non-incident acute pancreatitis ( <i>N</i> = 486 629)
<b>Age</b>	57.04 (8.09)	59.09 (7.75)	57.02 (8.09)
<b>Sex</b>			
Female	267 189 (54.6)	1569 (51.0)	265 620 (54.6)
Male	222 519 (45.4)	1510 (49.0)	221 009 (45.4)
<b>Townsend deprivation index category</b>			
Low deprivation	163 224 (33.3)	1241 (40.3)	161 983 (33.3)
Moderate deprivation	163 243 (33.3)	857 (27.8)	162 386 (33.4)
High deprivation	163 241 (33.3)	981 (31.9)	162 260 (33.3)
<b>Level of education</b>			
Below college	330 258 (67.4)	2355 (76.5)	327 903 (67.4)
Above college	159 450 (32.6)	724 (23.5)	158 726 (32.6)
<b>Ethnicity</b>			
Others	24 665 (5.0)	132 (4.3)	24 533 (5.0)
White	465 043 (95.0)	2947 (95.7)	462 096 (95.0)
<b>Ever smoking</b>			
Never smoking	269 161 (55.0)	1463 (47.5)	267 698 (55.0)
Previous/current	220 547 (45.0)	1616 (52.5)	218 931 (45.0)
<b>Current drinker</b>			
No	38 164 (7.8)	344 (11.2)	37 820 (7.8)
Yes	451 544 (92.2)	2735 (88.8)	448 809 (92.2)
<b>Alcohol intake frequency</b>			
Less than once a week	148 821 (30.4)	1182 (38.4)	147 639 (30.3)
Once or twice a week	126 516 (25.8)	766 (24.9)	125 750 (25.8)
Three or four times a week	113 898 (23.3)	577 (18.7)	113 321 (23.3)
Daily or almost daily	100 473 (20.5)	554 (18.0)	99 919 (20.5)
<b>Use of spread made with oil</b>			
Never/rarely use	57 123 (11.7)	56 817 (11.7)	306 (9.9)
Use	432 585 (88.3)	429 812 (88.3)	2773 (90.1)
<b>Dairy intake frequency</b>			
≥2 servings per day	197 388 (40.3)	196 015 (40.3)	1373 (44.6)
<2 servings per day	292 320 (59.7)	290 614 (59.7)	1706 (55.4)
<b>Physical activity (IPAQ)</b>			
Low	74 761 (15.3)	585 (19.0)	74 176 (15.2)
Moderate	161 648 (33.0)	939 (30.5)	160 709 (33.0)
High	159 946 (32.7)	859 (27.9)	159 087 (32.7)
Unknown	93 353 (19.1)	696 (22.6)	92 657 (19.0)
<b>BMI category</b>			
<25 kg m <sup>-2</sup>	161 921 (33.1)	644 (20.9)	161 277 (33.1)
25–29.9	118 164 (24.1)	1200 (39.0)	116 964 (24.0)
>30	209 623 (42.8)	1235 (40.1)	208 388 (42.8)
<b>Charlson comorbidity index</b>			
Mean (SD)	0.27 (0.90)	0.46 (1.08)	0.27 (0.90)
<b>Baseline gallstones</b>			
No	474 108 (96.8)	471 225 (96.8)	2883 (93.6)
Yes	15 600 (3.2)	15 404 (3.2)	196 (6.4)
<b>Sleep duration per day</b>			
<7 hours	124 291 (25.4)	864 (28.1)	123 427 (25.4)
7–8 hours	172 295 (35.2)	1168 (37.9)	171 127 (35.2)
>8 hours	193 122 (39.4)	1047 (34.0)	192 075 (39.5)
<b>Modified HEI score</b>			
Mean (SD)	2.29 (0.98)	2.29 (0.98)	2.15 (1.02)

SD, standard deviation; BMI, body mass index.



**Table 2** Associations between meat consumption and incident acute pancreatitis in the UK Biobank cohort

Meat (times per week)	Case/person-year	Mean intake <sup>c</sup> (g per day)	Minimally adjusted model <sup>a</sup>		Fully adjusted model <sup>b</sup>	
			HR (95% CI)	<i>P</i>	HR (95% CI)	<i>P</i>
<b>Processed meat</b>						
0–0.9	1061/2 601 942	11.82	Ref.		Ref.	
1–1.9	910/1 892 628	20.00	<b>1.15 (1.05, 1.26)</b>	<b>0.003</b>	<b>1.10 (1.00, 1.21)</b>	<b>0.041</b>
2–4	958/1 739 278	26.74	<b>1.32 (1.20, 1.44)</b>	<b>&lt;0.001</b>	<b>1.18 (1.07, 1.29)</b>	<b>0.001</b>
>4	150/248 842	36.57	<b>1.48 (1.24, 1.77)</b>	<b>&lt;0.001</b>	<b>1.24 (1.04, 1.49)</b>	<b>0.018</b>
<i>P</i> trend	—	—	—	<b>&lt;0.001</b>	—	<b>&lt;0.001</b>
Per 25 g per day	—	—	<b>1.54 (1.35, 1.76)</b>	<b>&lt;0.001</b>	<b>1.29 (1.12, 1.47)</b>	<b>&lt;0.001</b>
<b>Unprocessed red meat</b>						
0–0.9	258/661 154	6.40	Ref.		Ref.	
1–1.9	1135/2 557 794	32.10	1.10 (0.96, 1.27)	0.164	1.02 (0.88, 1.17)	0.822
2–4	1407/2 728 100	45.42	<b>1.23 (1.07, 1.41)</b>	<b>0.003</b>	1.10 (0.96, 1.27)	0.158
>4	279/535 641	59.92	<b>1.21 (1.02, 1.45)</b>	<b>0.032</b>	1.05 (0.88, 1.25)	0.609
<i>P</i> trend	—	—	—	<b>0.001</b>	—	0.113
Per 25 g per day	—	—	<b>1.13 (1.05, 1.21)</b>	<b>0.001</b>	1.06 (0.98, 1.14)	0.135
<b>Poultry</b>						
0–0.9	470/1 022 346	10.94	Ref.		Ref.	
1–1.9	1081/2 320 086	25.45	0.99 (0.89, 1.11)	0.858	0.98 (0.88, 1.10)	0.745
2–4	1464/2 994 642	36.36	1.09 (0.98, 1.21)	0.122	1.08 (0.97, 1.20)	0.155
>4	64/145 615	58.06	1.05 (0.80, 1.37)	0.745	0.99 (0.75, 1.29)	0.915
<i>P</i> trend	—	—	—	<b>0.047</b>	—	0.075
Per 25 g per day	—	—	1.09 (0.99, 1.19)	0.074	1.07 (0.98, 1.18)	0.13
<b>Fish</b>						
0–0.9	300/496 408	5.15	Ref.		Ref.	
1–1.9	1249/2 600 375	20.96	<b>0.73 (0.64, 0.83)</b>	<b>&lt;0.001</b>	<b>0.80 (0.71, 0.92)</b>	<b>0.001</b>
2–4	1303/2 944 295	33.18	<b>0.63 (0.55, 0.72)</b>	<b>&lt;0.001</b>	<b>0.75 (0.66, 0.86)</b>	<b>&lt;0.001</b>
>4	227/441 611	51.78	<b>0.73 (0.61, 0.87)</b>	<b>0.001</b>	0.87 (0.73, 1.04)	0.125
<i>P</i> trend	—	—	—	<b>&lt;0.001</b>	—	<b>0.013</b>
Per 25 g per day	—	—	<b>0.80 (0.73, 0.87)</b>	<b>&lt;0.001</b>	<b>0.78 (0.68, 0.89)</b>	<b>&lt;0.001</b>

<sup>a</sup>The minimally adjusted model adjusted for age, sex, and ethnicity. <sup>b</sup>The fully adjusted model was further adjusted for TDI, education level, physical activity level, body mass index, smoking status, alcohol drinking status, and modified HEI score. <sup>c</sup>Meat intake (g) per day was calculated by the mean intake of the subgroups of participants who had at least two WebQ records ( $N = 102\,612$ ) stratified by meat intake frequency. HR, hazard ratio; CI, confidence interval.

### 3.2 Primary analysis

Table 2 shows the association between the consumption of subtypes of meat and incident AP, with all models satisfying the proportional hazard assumptions ( $P$ -values  $>0.05$ ). In the fully adjusted model, higher consumption of processed meat is associated with a higher risk of incident AP (per 25 g per d: HR: 1.29, 95% CI: 1.12–1.47). In contrast, higher consumption of fish intake is associated with a lower risk of AP (per 25 g per d: HR: 0.78, 95% CI: 0.68–0.89). No significant associations were observed between unprocessed meat and poultry intake and the risk of AP.

### 3.3 Secondary analyses

In the substitution analysis, data showed that replacing 1, 2, and 3 servings of processed meat with fish per week was associated with 6% (95% CI: 2%–9%), 11% (95% CI: 4%–17%), and 16% (95% CI: 6%–24%) reduced risk of incident AP. No significant relationships were found when unprocessed red meat was substituted with fish (Table 3).

When analyzing the associations of unprocessed beef and pork separately, we found that only a 1–1.9 times per week intake for these three types of meat contributed to increased AP, which was 10% for beef (95% CI: 2%–19%)

**Table 3** Substitution analysis of replacing 1, 2, or 3 servings per week of processed or unprocessed red meat with isocaloric servings of fish and the associated risk of incident acute pancreatitis

	HR (95% CI)	<i>P</i>
<b>Substitution of processed meat</b>		
<b>Leave-one-out model 1<sup>a</sup></b>		
Replaced by 1 serving fish per week	<b>0.94 (0.91, 0.98)</b>	<b>0.003</b>
Replaced by 2 serving fish per week	<b>0.89 (0.83, 0.96)</b>	<b>0.001</b>
Replaced by 3 serving fish per week	<b>0.84 (0.76, 0.94)</b>	<b>0.003</b>
<b>Substitution of unprocessed red meat</b>		
<b>Leave-one-out model 2<sup>b</sup></b>		
Replaced by 1 serving fish per week	0.98 (0.95, 1.02)	0.265
Replaced by 2 serving fish per week	0.96 (0.90, 1.03)	0.236
Replaced by 3 serving fish per week	0.95 (0.85, 1.05)	0.341

<sup>a</sup>Leave-one-out model 1 included fish consumption, unprocessed red meat consumption, poultry consumption, total meat intake and all the covariates in the fully adjusted model. <sup>b</sup>Leave-one-out model 2 included fish consumption, processed meat consumption, poultry consumption, total meat intake and all the covariates in the fully adjusted model.

and 13% for pork. Oppositely, a 1–1.9 times per week intake of oily fish, compared to the reference group, resulted in a 11% decreased risk of incident AP (95% CI: 3%–18%) (Table S1†).



### 3.4 Subgroup and sensitivity analyses

Similar associations were observed in most subgroup analyses (Tables S2–S4†), yet there were significant interactions between processed meat consumption and ethnicity (Table S2,†  $P_{\text{interaction}} = 0.034$ ) and poultry and ethnicity (Table S2,†  $P_{\text{interaction}} = 0.006$ ).

Our results remained robust in most of the sensitivity analyses (Tables S5–S13†). The association persisted when we adjusted for CCI, sleep duration, alcohol intake frequency (Table S5†), oil use and dairy intake (Table S6†). Associations remained when we further incorporated baseline cholecystectomy and gallstone status and blood triglyceride level as covariates (Table S7†), considered the mutually adjusted model (Table S8†), treated TDI, BMI and sleep duration as continuous variables (Table S9†), excluded the first one, two, and three years (Table S10†), used '0.1–0.9 times per week' as the referent category (Table S11†), reprocessed the covariates with multiple imputations (Table S12†), and reconstructed an age-scaled Cox regression model to verify the meat–AP relationship (Table S13†).

### 3.5 Mediation analysis

In the mediation analysis, we observed that baseline blood triglyceride levels accounted for 21.12% (95% CI: 15.9%–30.0%) of the adverse effect of processed meat intake and 10.89% (95% CI: 7.17%–22.90%,  $P < 0.001$ ) of the protective effect of fish consumption on acute pancreatitis (Table S14 and Fig. S1†).

## 4. Discussion

In this study, we found that more frequent intake of processed meat was associated with an increased risk of incident AP, while more frequent intake of fish was linked to a decreased risk. Furthermore, replacing processed meat consumption with fish was associated with a reduced risk of incident AP. At the same time, there were no significant associations between either unprocessed meat or poultry consumption and AP risk. The observed findings remained consistent in most subgroup and sensitivity analyses.

Previous studies have examined the associations between meat consumption and pancreatic diseases, especially pancreatic cancer. Nevertheless, no consensus has been reached.<sup>18,37–39</sup> For processed meat consumption, the Multiethnic Cohort Study showed red meat and processed meat consumption to be strong risk factors for exocrine pancreatic cancer with an associated 50–70% increased risk across quintiles.<sup>37</sup> Our study focused on incident acute pancreatitis and discovered a significant relationship between processed meat and the disease (per 25 g per d: HR: 1.29, 95% CI: 1.12–1.47), in accordance with two US cohort studies that highlighted diets rich in saturated fat and cholesterol were associated with gallstone-related AP.<sup>13,14</sup> When it comes to fish consumption, a cohort study observed a significant inverse association between total fish consumption  $\leq 2.0$ – $3.0$  servings per

week and the risk of non-gallstone-related acute pancreatitis,<sup>19</sup> indicating fish consumption as a protective factor. Our study revealed a similar inverse association, especially at 2–4 times per week.

Our results regarding red meat consumption were inconsistent with those of a previous study,<sup>14</sup> which showed that red meat consumption was positively associated with gallstone-related AP ( $P$  trend  $< 0.0001$ ) and recurrent AP ( $P$  trend = 0.02) among 145 886 participants in the Multiethnic Cohort Study. The discrepancy may partially be attributed to a relatively smaller sample size of that study and its different study design, which did not separately analyze processed and unprocessed red meat. Evidence on poultry consumption is still lacking, and further investigation is needed to determine if poultry consumption is associated with the risk of AP.

A series of potential mechanisms could explain the impact of processed meat and fish on incident AP, respectively. Certain chemicals produced during meat processing may explain the increased risk of processed meat. Firstly, the effect of dietary nitrate, nitrite, and NOCs along with PAHs rich in processed meat has been unanimously confirmed.<sup>40–43</sup> Chemical reactions exist in the gastrointestinal tract, where nitrate is reduced to nitrite by the gut bacterial flora, and then nitrite may react with nitration precursors (amines, amides, *etc.*) to form NOCs,<sup>44</sup> which is considered to have a selective cytotoxic effect on pancreatic  $\beta$ -cells, leading to pancreatic ductular inflammation.<sup>45,46</sup> Secondly, PAHs, produced during preparation, and processing involving high temperatures<sup>47</sup> (grilling, smoking, toasting, roasting, and frying) are likely to be involved in the pathological mechanism of AP. In an animal experiment, researchers demonstrated that low-dose developmental oxygenated PAH (OPAH) exposure impairs early  $\beta$ -cell differentiation in zebrafish by altering DNA methylation and gene expression, resulting in endocrine disruption of the pancreas.<sup>48</sup> However, whether a similar mechanism occurs in the pathology process of AP in humans requires further investigation. In addition, as these toxic chemicals are produced only during meat processing, it is reasonable to assume that unprocessed red meat may be less harmful, which aligns with our results. Thirdly, the roles of saturated dietary fat are crucial as well, since it has been reported that triglycerides at high levels are strongly associated with acute pancreatitis,<sup>49</sup> probably because it induces pancreatic acinar lipotoxicity and cellular stress.<sup>50,51</sup> As is revealed in an animal trial, intrapancreatic fat would induce necrotic cell death through intracellular calcium release and inhibition of mitochondrial complexes I and V.<sup>52</sup>

Additionally, our mediation analysis, which suggests that blood triglyceride levels may play a role in the relationship between fish consumption and the risk of AP, provides a novel perspective on the potential biological mechanisms underlying these associations. Further research is needed to explore the significance of triglycerides in the pathway from dietary habits to the development of AP, and to uncover the precise mechanisms by which dietary fats and their metabolites affect pancreatic health. Understanding these mechanisms could be



instrumental in developing dietary interventions aimed at reducing the risk of AP through lipid level management.

When oily fish intake and non-oily fish intake were separately analyzed, we discovered that only oily fish intake (1–1.9 times per week) was associated with a decreased risk of incident AP. It denoted the potential protective mechanism of n-3 polyunsaturated fatty acids (PUFAs) rich in oily fish, especially alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), docosapentaenoic acid (DPA) and docosahexaenoic acid (DHA). A Japanese research study demonstrated that individuals in the highest quartiles of marine n-3 PUFA and DHA consumption had a 30% decreased risk of pancreatic cancer, compared with those in the lowest quartile.<sup>53</sup> Since they serve as anti-inflammatory compounds and antioxidants,<sup>19</sup> it's reasonable to suggest that they attenuate the levels of inflammatory cytokines (IL-6, IL-1 $\beta$  and TNF- $\alpha$ ) and reactive oxygen species (ROS), which have been revealed to be important in the pathogenesis of AP.<sup>54</sup>

The results of the current study highlighted the importance of adjusting meat ingestion structure to prevent the onset of AP. Of note, we observed significantly decreased risks when we replaced one, two, and three servings per week of processed meat with fish. Our study offers new choices of food patterns for people seeking an optimal food composition of diet while keeping total meat intake unchanged. However, as food substitution inevitably encompasses the replacement of behaviors, and brings amplified confounding, the observed beneficial effect should be interpreted cautiously.

Within the scope of our knowledge, this is the largest study in sample size focusing on the association between consumption of different types of meat collectively and incident AP. The strengths of this study are as follows. Firstly, given the low incidence rate of AP,<sup>55</sup> we leveraged data from the cohort with a large sample size from the UK Biobank, assuring statistical efficacy. Secondly, potential confounding was optimally attenuated *via* multiple adjustments and sensitivity analyses.

Several limitations of our study still exist. First, we acknowledge a limitation regarding the identification of AP cases using ICD codes. As highlighted in previous research, the positive predictive value of ICD codes for identifying AP cases is approximately 0.78, indicating potential misclassification. Additionally, a significant proportion of AP cases in the UK Biobank lack specific etiology codes, which may affect the precision of our analyses. We have carefully considered these limitations and recommend that future research incorporates more detailed validation of AP cases to enhance the accuracy of case identification.

Second, given a lack of literature on the associations between dietary factors and incident AP, the covariates may not include all possible confounding factors, which could introduce bias into the results. Additionally, the categorization of some continuous variables may potentially lead to information loss and reduced statistical power. We chose to categorize variables like BMI primarily due to the consideration that the relationship between BMI and the risk of pancreatitis may not be linear. Categorizing these variables allows us to more

effectively evaluate their impact on pancreatitis risk within different clinically relevant ranges.

Third, the generalizability of our findings required further investigation. While the UK Biobank cohort, comprising individuals aged 40–69 years at the baseline, almost overlaps with the age distribution in the Europeans with an interquartile range of 45–74 years,<sup>2</sup> our findings may have limited generalizability to younger populations or specific subgroups with distinct age-related risk profiles for AP. Furthermore, to address potential age-related biases, we conducted sensitivity analyses using an age-scaled model. This adjustment helps ensure our findings are not unduly influenced by age differences, enhancing the reliability of our results. However, the generalizability to younger populations still warrants further investigation. This limitation should be considered when interpreting the study results and applying them to broader clinical contexts.

Additionally, the leave-one-out model used in this study, which controls total intake of all four types of meat but does not account for total energy intake due to limitations in our data, also acknowledges a methodological limitation. Despite this, our results provide significant guidance on dietary patterns, provided the analytical methods are clearly and properly demonstrated.

## 5. Conclusions

In summary, we found that more frequent consumption of processed meat was associated with a 29% or greater elevated risk of incident AP. Conversely, more frequent consumption of fish was associated with a 25% decreased AP risk. No significant associations were observed for unprocessed red meat and poultry. Notably, replacing one, two, and three servings per week of processed meat with fish was associated with a 6%, 11%, and 16% decreased AP risk. These findings suggested that a diet rich in fish and low in processed meat, or a diet that substitutes processed meat with fish may mitigate the risk of incident AP, which the general population at risk may consider carefully adjusting meat ingestion structure as a preventive strategy against the onset of AP.

## Author contributions

Tianyi Che (conceptualization: equal; design: equal; methodology: equal). Qijia Gong (design: equal; visualization: equal; writing – original draft: leading; writing – review & editing: leading). Jiawei Geng (conceptualization: equal; design: leading; methodology: leading). Tian Fu (methodology: supporting; investigation: equal; writing – review & editing: supporting). Sidan Wang (methodology: supporting; resources: supporting; writing – review & editing: supporting). Yao Zhang (methodology: supporting; investigation: supporting; writing – review & editing: supporting). Jianfeng Yang (methodology: supporting; investigation: supporting; writing – review & editing: supporting). Xiaofeng Zhang (methodology: support-



ing; investigation: supporting; writing – review & editing: equal). Lintao Dan (design: equal; methodology: equal; writing – review & editing: equal). Jie Chen (conceptualization: leading; design: leading; methodology: equal; formal analysis: leading; writing – review & editing: supporting). Chunhua Zhou (conceptualization: leading; funding acquisition: leading; project administration: leading; writing – review & editing: supporting).

## Conflicts of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Ethical approval and consent to participate

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

## Data availability

The data sets used in the current study are available in a public, open-access repository (<https://www.ukbiobank.ac.uk/>).

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