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Dietary Factors Reduce Risk of Acute Pancreatitis in a Large Multiethnic Cohort

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Abstract

Background & Aims—Pancreatitis is a source of substantial morbidity and health cost in the United States. Little is known about how diet might contribute its pathogenesis. To characterize dietary factors that are associated with risk of pancreatitis, by disease subtype, we conducted a prospective analysis of 145,886 African Americans, Native Hawaiians, Japanese Americans, Latinos, and whites in the Multiethnic Cohort.

Methods—In the Multiethnic Cohort (45–75 years old at baseline), we identified cases of pancreatitis using hospitalization claim files from 1993 through 2012. Patients were categorized as having gallstone-related acute pancreatitis (AP) (n=1210), AP not related to gallstones (n=1222), or recurrent acute pancreatitis or suspected chronic pancreatitis (n=378). Diet information was obtained from a questionnaire administered when the study began. Associations were estimated by hazard ratios and 95% CIs using Cox proportional hazard models adjusted for confounders.

Results—Dietary intakes of saturated fat (*P* trend=.0011) and cholesterol (*P* trend=.0008) and their food sources, including red meat (*P* trend<.0001) and eggs (*P* trend=.0052), were positively

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associated with gallstone-related AP. Fiber intake, however, was inversely associated with gallstone-related AP (*P* trend=.0005) and AP not related to gallstones (*P* trend=.0035). Vitamin D, mainly from milk, was inversely associated with gallstone-related AP (*P* trend=.0015) whereas coffee consumption protected against AP not related to gallstones (*P* trend<.0001). With the exception of red meat, no other dietary factors were associated with recurrent acute or suspected chronic pancreatitis.

Conclusions—Associations between dietary factors and pancreatitis were mainly observed for gallstone-related AP. Interestingly, dietary fiber protected against AP, related and unrelated to gallstones. Coffee drinking protected against AP not associated with gallstones. Further studies are warranted to confirm our findings.

Keywords

pancreas; population; epidemiology

INTRODUCTION

Pancreatitis is a source of substantial morbidity and health cost in the United States[1]. Gallstones are the most common cause of AP, and cholecystectomy eliminates the risk of recurrent episodes[2]. Recurrent AP (RAP), mostly non-gallstone related, can progress to chronic pancreatitis (CP), a serious condition which can severely impact quality of life[3] and lead to serious long-term complications, including diabetes and pancreatic cancer[2].

Currently there is no available treatment for pancreatitis which underscores the importance of identifying modifiable risk factors for primary prevention of this disease. It is reasonable to expect that diet plays a role in the etiology of digestive diseases including pancreatitis[2]. The literature on dietary associations is very limited; other than alcohol abuse, no convincing dietary factors for pancreatitis have been reported[2].

To our knowledge, there have been no population-based prospective studies that have evaluated the association of dietary factors with pancreatitis subtypes (GS AP, non-GS AP, RAP/CP) in multiethnic populations in the US. Thus, in this study of a large number of pancreatitis cases, we investigated dietary hypotheses by pancreatitis type among African Americans, Native Hawaiians, Japanese Americans, Latinos and whites participating in the Multiethnic Cohort (MEC) Study.

SUBJECTS AND METHODS

Study population

The MEC is a prospective cohort of >215,000 men and women enrolled between 1993 and 1996 at the age of 45-75 years. The MEC study design and characteristics have been described in detail previously[4]. The baseline questionnaire assessed diet, lifestyle, anthropometrics, family and personal medical history. Since baseline, there have been four follow-up questionnaires. Incident cancers in the cohort are identified through annual linkage to the SEER tumor registries in Hawaii and California. Deaths are determined through annual linkage to state death files in California and Hawaii, and periodic linkage to the National Death Index. Participants older than 65 years were linked to Centers for Medicare Services (CMS) claims (1999-2012) using Social Security number, sex, and date of birth, and 93% of these participants were linked[5]. California participants were also linked to the Office of Statewide Health Planning and Development Hospital Discharge Data. The Institutional Review Boards at the University of Southern California and the University of Hawaii approved this study.

For this study, participants with a diagnosis of pancreatic cancer or a diagnosis of pancreatitis identified via the California hospital discharge data (CHDD) (N=361) before cohort entry were excluded. We also excluded participants (N=26,070) who were not from the five major ethnic groups or who had missing baseline information on risk factors and important covariates. HI participants who were not Medicare members (N=14,035) or who were not fee-for-service (FFS) members (N=28,438) were excluded, as we had no opportunity to discover a pancreatitis diagnosis in this group. A total of 145,886 eligible participants were available for analysis.

Case ascertainment

As previously described[6], pancreatitis cases were ascertained from the Medicare hospitalization claim files (MedPAR) between 1999 and 2012 among FFS participants using the principal diagnosis in the claim with an International Classification of Diseases (ICD), 9th Revision, code of 577.0 or 577.1. For California participants, we also utilized the CHDD between 1993 and 2012 to identify cases using the same codes as above. Pancreatitis cases were categorized as acute pancreatitis (AP) if they had one hospitalization with code 577.0. We further divided the AP cases into gallstone and non-gallstone related subtypes based on ICD-9 codes for gallstone (574.x) from the same pancreatitis hospitalization claim or procedure codes for cholecystectomy [ICD-9: 51.2x and Current Procedural Terminology codes: 47480, 47490, 47562, 47563, 47564, 47600, 47605, 47610, 47612, 47620, 56340, 56341, 56342]. We categorized pancreatitis cases as recurrent AP (RAP) if they had >1 hospitalization with code 577.0 >30 days apart with no concurrent gallstone related diagnosis, and as suspected CP (SCP) if they had ≥2 hospitalizations with code 577.1 ≥60 days apart. For each case, the date of the first hospitalization claim where pancreatitis was the principal diagnosis was used as the sentinel event date. A total of 2,814 cases were identified through 2012; 4 cases were excluded because we could not identify matched non-cases using the criteria below.

Exposure assessment

Diet, physical activity, demographic and other known/potential risk factors for pancreatitis including alcohol intake, smoking history, anthropometry, and self-report of physician-diagnosed type 2 diabetes, were obtained from the baseline questionnaire. Dietary information was obtained using a Quantitative FFQ (QFFQ) designed for use in this multiethnic population[4]. The QFFQ asked respondents to report how often they consumed particular foods and beverages during the past year and the usual portion size. Usual intake was reported by marking one of the following eight frequencies: never or hardly ever; once a month; 2 to 3 times a month; once a week; 2 to 3 times a week; 4 to 6 times a week; once a day; 2 or more times a day. A calibration study of the QFFQ was conducted using three 24 hour recalls from a random sub-sample of participants and revealed a high correlation between the QFFQ and 24 hour recalls for energy-adjusted nutrients in all sex–racial/ethnic groups[7]. In a subcohort (n= 99,085) that responded to a repeat QFFQ an average of 11.0 years after the baseline QFFQ, we found that while some dietary changes occurred, there was reasonably good concordance between quartiles of dietary intakes between the two measures (40% in the same quartile and 80% within +/− 1 quartile for most nutrients). All dietary fiber values presented in the tables, including values for soluble and insoluble fractions, were food composition values obtained by the Englyst procedure which aims to measure plant cell wall non-starch polysaccharides as the sum of the chemically identified constituent sugars; the procedure does not measure lignin[8]. Measures of dietary fiber intake determined from specific food sources (fruit, vegetable, cereal, legumes) are mutually exclusive. With the exception of coffee, dietary intakes were energy adjusted by the use of nutrient densities and were categorized into quartiles. Cutpoints were determined by the distribution in all participants; the lowest quartile of intake was the reference category. Coffee intake was categorized as none, >0 and ≤1, 2-3, ≥4 cups/day.

Statistical analysis

As the time of diagnosis was not measured precisely, but was based on hospital admission date, we used a Cox proportional hazards model for interval data based on a logistic model with a complementary log-log link[9]. For each case, we constructed the set of at-risk individuals (alive and without a pancreatitis diagnosis at the date of index case's diagnosis) matched on ethnicity, sex, exact birth year, study area (CA or HI), and, if a case was identified via Medicare, length of Medicare coverage (± 1 year). Participants with a history of cholecystectomy, identified either from the baseline questionnaire or claims, were not eligible to be selected as controls for GS AP risk sets. The associations between dietary factors and pancreatitis were estimated by the hazard ratio (HR) and its 95% confidence interval (CI) adjusted for education (≤high school, some college, college graduate or higher), BMI (continuous), history of diabetes (no/yes), smoking-pack-years (never, past <20, past ≥20, current <20, current ≥20), alcohol intake (non-drinkers, >0 and <24, 24−≤48, and >48 g ethanol/day), vigorous activity (continuous), and caloric intake (continuous). Tests for trend were performed by entering the ordinal values (*i.e.*, 1,2,3) representing categories of exposures as continuous variables in the models. All analyses were conducted using SAS version 9.3 (SAS Institute, Inc., Cary, NC). All P values were two-sided.

RESULTS

The characteristics of the study population are shown in Table 1. The majority of participants were female and aged 55 and older at cohort entry. The ethnic breakdown was 26.9% Latinos, 25.3% Japanese Americans, 22.5% whites, 20.5% African Americans, and 4.9% Native Hawaiians. At baseline, 15.9% were current smokers, 12.0% were diabetics, 20.8% were obese, and 48.8% drank alcohol. A total of 2,810 pancreatitis cases were identified among these participants: 1,210 gallstone-related (GS) AP (43.1%), 1,222 non-GS AP (43.5%), and 378 RAP/SCP (13.5%). The average age at cohort entry and at the sentinel event was similar between GS and non-GS AP cases, while younger for RAP/SCP cases. The means of hospitalization days were 6.2, 5.8, and 7.1 for GS AP, non-GS AP, and RAP/

SCP, respectively. The RAP/SCP cases were more likely to be current smokers, diabetic, and drink a high quantity of alcohol compared to the GS and non-GS AP cases.

Diet and nutrient intakes vary across ethnic groups (Supplemental Table 1). African Americans reported the highest intake of cholesterol and Japanese Americans the lowest. African Americans also had the lowest intakes of vegetables and coffee. US-born Latinos and African Americans reported the highest intakes of saturated fat. The highest intake of red meat was observed in US-born Latinos and Native Hawaiians. Non US-born Latinos reported the highest intakes of dietary fiber and vegetables. Whites reported the highest intake of vitamin D compared to the other ethnic groups.

Table 2 shows the associations between consumption of red meat, fish, eggs, saturated fat and cholesterol and pancreatitis. Red meat intake was positively associated with GS AP (*P* trend<.0001); comparing the highest quartile to the lowest, the HR of GS AP was 1.46 (95% CI: 1.22, 1.74). Red meat was also associated with an increased risk of RAP/SCP (*P* trend=.02), but the HR comparing the highest quartile with the lowest did not reach statistical significance (HR=1.36; 95% CI: 0.99, 1.87). We found an increased risk of GS AP associated with egg (*P* trend=.0052), saturated fat (*P* trend=.0011) and cholesterol (*P* trend=.0008) intakes. No association was observed between consumption of red meat, fish, eggs, omega-3 fatty acids, saturated fat and cholesterol with non-GS AP.

Table 3 shows the association between intakes of fiber, fruits, vegetables, legumes and pancreatitis. Total dietary fiber was inversely associated with both GS AP (*P* trend=.0005) and non-GS AP (*P* trend=0.0035). Because of the strong protective association of total dietary fiber, we further examined the association of soluble, insoluble fiber and specific food sources of fiber with pancreatitis.

There was a significant inverse association with both fiber sub-types for GS and non-GS AP (soluble fiber *P* trend ≤.0494 and insoluble fiber *P* trend ≤.0012). We found a significant trend for dietary fiber from fruits (*P* trend=.0406) and fruit intake (*P* trend=.0230) and a suggestive trend for vegetable intake (*P* trend=.0582) for GS AP, but the HRs did not reach statistical significance. Other specific food sources of fiber (*i.e.,* legumes and grains) were not associated with pancreatitis. Further adjustment for meat intake did not change the results substantially (data not shown).

We found that coffee drinking was inversely associated with non-GS AP (*P* trend<.0001) and possibly with non-GS RAP/SCP (*P* trend=.05) (Table 4). Caffeine was inversely associated with non-GS AP and RAP/SCP, but after coffee was included in the model, the associations disappeared. Decaffeinated coffee was not associated with any pancreatitis subtype (data not shown). Increasing vitamin D (*P* trend=.0015) and milk intakes (*P* trend=.0071) were inversely associated with GS AP.

The ethnic specific results for diet-pancreatitis associations are shown in Supplemental Table 2.

DISCUSSION

To our knowledge, this study is the largest population-based prospective analysis of dietary factors for pancreatitis in the US. Our results show that the majority of dietary factors are mainly associated with the risk of GS related AP, with the notable exception of dietary fiber and coffee intakes which are associated with reduced risk of non-GS AP and RAP/SCP.

We noted several interesting diet associations with GS AP in our study. Diet rich in saturated fat and cholesterol (*e.g.,* eggs and red meat) were associated with a higher risk of GS AP, while intakes of vitamin D, milk, and fruits were associated with a reduced risk. Our results are consistent with findings from the Iowa Women's Health Study which show that intakes of total and saturated fat were associated with an increased risk of AP[10]. A previous systematic review suggests that in humans, a prolonged exposure to a high-fat diet may work synergistically with gallstones to trigger an AP attack indicating a possible role of diet as a cofactor in the causation of AP[11]. We also found that a high-cholesterol diet was associated with the risk of GS AP. Both animal and population-based studies have identified high fat and cholesterol diets to be risk factors for gallstone formation[12, 13]. No study has previously shown an association between dietary cholesterol and pancreatitis.

We found dietary fiber to be inversely associated with both GS and non-GS AP. Fiber has been associated with changes in gut microbiota, improvements in gut epithelial tightness and prevention of endotoxin transit into the system[14, 15]. Importantly, experimental animal models of pancreatitis show that endotoxin can promote the development and severity of pancreatitis[16, 17]. Insoluble fiber may also have a protective effect by reducing the development of gallstones[18], a major cause of AP. A previous analysis in the Iowa Women's Health Study, however, did not show an association between crude fiber intake with either AP or CP[10].

We found a suggestive inverse association of vegetable and fruit intakes with the risk of GS AP. While speculative, the protective associations are biologically plausible since vegetables and fruits have a high content of antioxidants, and reactive oxygen and nitrogen species have been implicated in the pathogenesis of pancreatitis[19]. Diets high in vegetables and fruits have also been shown to reduce risks of gallstone and cholecystectomy[20], therefore, it is possible that the diet-GS AP association is mediated by cholelithiasis.

We found that increased intakes of vitamin D and milk were inversely associated with GS AP. In a cross-sectional study, vitamin D deficiency was correlated with CP[21]. A recent murine study revealed that vitamin D receptor-directed treatment reduces fibrosis and inflammation in both AP and CP[22]. We are unaware of any previous report on dietary vitamin D and risk of pancreatitis.

A Swedish cohort reported a protective association between fish consumption and non-GS AP[23]. The authors hypothesized that the protective association was due to the anti-inflammatory and antioxidative properties of the long chain n-3 polyunsaturated fatty acids found in fish[23]. We did not find an association with omega-3 fatty acids or with fish intake in all ethnic groups combined; however, in the ethnic-specific analysis, an inverse association between fish intake and GS AP was observed in Caucasians (Quartile 4:Quartile 1 HR=0.58 (95% CI: 0.38, 0.88; P trend=0.01) – the same population as in the Swedish cohort.

We found that coffee intake was inversely associated with non-GS AP and RAP/SCP in a dose-dependent manner. The inverse association between coffee and pancreatitis is biologically plausible because coffee is associated with reduced diabetes incidence[24, 25] which is a risk factor for pancreatitis, particularly for RAP/SCP. Coffee also contains antioxidant and anti-inflammatory properties[26]. In an experimental model of pancreatitis, caffeine has been shown to have protective effects by inhibiting pathologic calcium signaling in the pancreatic acinar cell[27]. Two studies have examined the association between coffee drinking and pancreatitis and found conflicting results[28, 29]. The earlier prospective study in the US observed an inverse association of coffee intake with alcohol-related pancreatitis, and not with GS related pancreatitis[28]. This study similar to ours only included hospitalized cases, but unlike ours it did not differentiate between AP and CP. The more recent study based on prospective data in Sweden which focused on non-GS AP found no association with coffee consumption[29].

The strengths of our study include its prospective and population-based design, ethnic diversity, long follow up, large size, and detailed information on known/potential risk factors. There are several limitations. Measurement error in self-reported diet is inevitable and may have led to some degree of non-differential misclassification of exposures. While the concordance between baseline and follow data for dietary factors in the MEC was good, changes in diet over time would be more likely to attenuate disease associations than to create spurious ones. The algorithm used to identify pancreatitis cases using Medicare/ CHDD databases has not been validated in the MEC. Previous studies have used similar databases to identify pancreatitis cases[10, 30-33]; the sensitivity, specificity, and positive and negative predictive values of AP primary discharge diagnosis code were 96%, 85%, 80%, and 98%, respectively[33]. A recent paper showed that using ICD-9-CM code as the sole basis to identify CP cases may overestimate CP diagnosis[34]. While using two different CP hospitalization claims may improve the specificity in our study, given the complexity of CP clinical diagnosis and lack of access to medical records, we can only call the CP cases “suspected CP”. Disease misclassification, therefore, might have occurred; however, because it would be irrespective of exposures, the potential bias would be toward the null.

In conclusion, our study indicated that several dietary factors including red meat, saturated fat, cholesterol, coffee, fiber, vitamin D, fruits and vegetables might be associated with pancreatitis, warranting confirmation in other studies. Given the lack of an effective treatment of pancreatitis, studies to determine the effectiveness of dietary factor interventions are warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

AP	acute pancreatitis
BMI	body mass index
CI	confidence interval
CP	chronic pancreatitis
GS	gallstone
HR	hazard ratio
RAP	recurrent acute pancreatitis

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Table 1

Baseline characteristics of pancreatitis cases and study participants

	GS AP (n = 1,210)		Non-GS AP (n = 1,222)		Non-GS RAP/SCP (n = 378)		All (n = 145,886)	
	No.	%	No.	%	No.	%	No.	%
Age at sentinel event, mean (SD)	73.8 (8.6)		73.3 (8.8)		70.6 (9.2)		---	
Years from cohort entry to sentinel event, mean (SD)	11.0 (5.1)		10.8 (5.2)		8.8 (5.4)		---	
Age at cohort entry, years								
45-54	216	17.9	222	18.2	87	23.0	41,861	28.7
55-64	471	38.9	481	39.4	141	37.3	53,142	36.4
65+	523	43.2	519	42.5	150	39.7	50,883	34.9
Race/ethnicity								
White	206	17.0	219	17.9	70	18.5	32,790	22.5
African American	259	21.4	364	29.8	120	31.8	29,867	20.5
Native Hawaiian	52	4.3	44	3.6	13	3.4	7,144	4.9
Japanese American	191	15.8	161	13.2	47	12.4	36,846	25.3
Latino – US-born	247	20.4	233	19.1	76	20.1	20,480	14.0
Latino – Non-US-born	255	21.1	201	16.4	52	13.8	18,759	12.9
Sex								
Men	513	42.4	508	41.6	147	38.9	65,063	44.6
Women	697	57.6	714	58.4	231	61.1	80,823	55.4
Smoking status								
Never	551	45.5	487	39.9	142	37.6	65,894	45.2
Past	507	41.9	492	40.3	144	38.1	56,860	39.0
Current	152	12.6	243	19.9	92	24.3	23,132	15.9
BMI (kg/m^2)								
<25	341	28.2	397	32.5	134	35.4	58,222	39.9
25-29.9	496	41.0	504	41.2	133	35.2	57,390	39.3
≥ 30	373	30.8	321	26.3	111	29.4	30,274	20.8
Diabetes								
No	997	82.4	993	81.3	293	77.5	128,453	88.1
Yes	213	17.6	229	18.7	85	22.5	17,433	11.9
Alcohol intake (ethanol g/day)								
None	732	60.5	685	56.1	227	60.1	74,718	51.2
>0 and < 24	387	32.0	422	34.5	115	30.4	55,482	38.0
24-≤ 48	59	4.9	56	4.6	12	3.2	9,833	6.7
> 48	32	2.6	59	4.8	24	6.3	5,853	4.0
Education								
≤ High School	668	55.2	634	51.9	200	52.9	64,739	44.4
Some college	330	27.3	354	29.0	105	27.8	43,472	29.8
College graduate	212	17.5	234	19.2	73	19.3	37,675	25.8

Table 2

Associations between meat, fish, fat intake* and pancreatitis

	GS AP		Non-GS AP		Non-GS RAP/SCP	
	No. Cases	**HR§ (95% CI)**	**No. Cases**	**HR§ (95% CI)**	**No. Cases**	**HR§ (95% CI)**
Total red meat						
≤ 14.4	233	1.00 (ref.)	267	1.00 (ref.)	74	1.00 (ref.)
> 14.4 – ≤ 24.5	286	1.22 (1.03-1.46)	306	1.12 (0.95-1.33)	77	1.04 (0.75-1.44)
> 24.5 – ≤ 36.3	289	1.26 (1.06-1.51)	282	1.03 (0.87-1.23)	101	1.37 (1.01-1.87)
> 36.3	339	1.46 (1.22-1.74)	300	1.04 (0.87-1.24)	102	1.36 (0.99-1.87)
p for trend		<0.0001		0.9128		0.0202
Fish excluding shellfish						
≤ 2.5	311	1.00 (ref.)	305	1.00 (ref.)	87	1.00 (ref.)
> 2.5 – ≤ 5.5	298	1.03 (0.88-1.21)	281	0.94 (0.80-1.11)	99	1.23 (0.92-1.65)
> 5.5 – ≤ 9.8	288	1.04 (0.88-1.23)	289	1.00 (0.84-1.18)	86	1.14 (0.84-1.55)
> 9.8	250	0.88 (0.73-1.05)	280	1.00 (0.84-1.19)	82	1.13 (0.82-1.56)
p for trend		0.2198		0.8405		0.5712
Shellfish						
≤ 0.2	290	1.00 (ref.)	290	1.00 (ref.)	84	1.00 (ref.)
> 0.2 – ≤ 1.0	287	1.01 (0.86-1.20)	291	1.03 (0.87-1.21)	100	1.27 (0.95-1.71)
> 1.0 – ≤ 2.5	298	1.08 (0.91-1.28)	279	1.04 (0.88-1.23)	93	1.29 (0.96-1.75)
> 2.5	272	1.02 (0.86-1.22)	295	1.11 (0.94-1.32)	77	1.12 (0.81-1.54)
p for trend		0.6226		0.2208		0.4675
Omega-3 fatty acids						
≤ 0.72	288	1.00 (ref.)	306	1.00 (ref.)	105	1.00 (ref.)
> 0.72 – ≤ 0.85	289	1.04 (0.87-1.23)	315	1.07 (0.91-1.27)	86	0.91 (0.67-1.22)
> 0.85 – ≤ 1.00	323	1.09 (0.92-1.29)	304	0.95 (0.80-1.12)	101	0.93 (0.70-1.25)
> 1.00	310	1.14 (0.96-1.36)	297	1.00 (0.84-1.18)	86	0.85 (0.63-1.16)
p for trend		0.1025		0.6342		0.3724
Eggs						
≤ 2.9	270	1.00 (ref.)	290	1.00 (ref.)	86	1.00 (ref.)
> 2.9 – ≤ 5.1	266	1.03 (0.87-1.22)	268	0.94 (0.79-1.11)	88	1.02 (0.75-1.38)
> 5.1 – ≤ 9.0	286	1.15 (0.97-1.36)	296	1.05 (0.89-1.23)	91	1.07 (0.79-1.44)
> 9.0	325	1.24 (1.05-1.47)	301	0.99 (0.84-1.17)	89	0.97 (0.71-1.31)
p for trend		0.0052		0.8094		0.9032
Percent of calories from saturated fat						
≤ 7.2	240	1.00 (ref.)	280	1.00 (ref.)	83	1.00 (ref.)
> 7.2 – ≤ 9.1	279	1.13 (0.95-1.36)	260	0.89 (0.75-1.06)	77	0.88 (0.64-1.21)
> 9.1 – ≤ 10.9	299	1.21 (1.01-1.45)	293	0.94 (0.79-1.12)	90	0.99 (0.72-1.35)
> 10.9	329	1.35 (1.12-1.62)	322	1.00 (0.83-1.19)	104	1.06 (0.77-1.46)
p for trend		0.0011		0.8082		0.5242

	GS AP		Non-GS AP		Non-GS RAP/SCP	
	No. Cases	HR[§] (95% CI)	No. Cases	HR[§] (95% CI)	No. Cases	HR[§] (95% CI)
Cholesterol						
≤ 79.0	242	1.00 (ref.)	270	1.00 (ref.)	87	1.00 (ref.)
> 79.0 – ≤ 103.2	279	1.18 (0.99-1.40)	274	0.98 (0.83-1.17)	83	0.94 (0.69-1.28)
> 103.2 – ≤ 130.6	311	1.32 (1.11-1.57)	296	1.03 (0.86-1.22)	84	0.90 (0.66-1.23)
> 130.6	315	1.33 (1.12-1.59)	315	1.03 (0.87-1.23)	100	1.02 (0.75-1.39)
p for trend		0.0008		0.6272		0.9393

[*] All intakes are reported as g/1000 kcal/day except for percent calories from saturated fat and cholesterol (mg/1000 kcal/day).

[§] HR adjusted for BMI, alcohol intake, diabetes, vigorous activity, education, smoking-pack years, and calories. Number of cases may not add up to the total cases in Table 1 due to missing values.

Table 3

Associations between intakes* of fiber, fruit, vegetable and vitamin D and pancreatitis

	GS AP		Non-GS AP		Non-GS RAP/SCP	
	No. Cases	HR§ (95% CI)	No. Cases	HR§ (95% CI)	No. Cases	HR§ (95% CI)
Total dietary fiber						
≤ 6.7	285	1.00 (ref.)	331	1.00 (ref.)	90	1.00 (ref.)
> 6.7 – ≤ 8.6	306	0.99 (0.83-1.16)	272	0.79 (0.67-0.94)	86	0.98 (0.72-1.33)
> 8.6 – ≤ 11.0	289	0.88 (0.74-1.05)	264	0.74 (0.62-0.87)	87	0.98 (0.71-1.33)
> 11.0	267	0.74 (0.62-0.89)	288	0.77 (0.65-0.92)	91	1.00 (0.72-1.38)
p for trend		0.0005		0.0035		0.9907
Insoluble fiber						
≤ 3.8	283	1.00 (ref.)	336	1.00 (ref.)	91	1.00 (ref.)
> 3.8 – ≤ 4.9	316	1.04 (0.88-1.22)	268	0.78 (0.66-0.92)	92	1.06 (0.79-1.43)
> 4.9 – ≤ 6.3	309	0.95 (0.80-1.12)	268	0.74 (0.62-0.87)	80	0.87 (0.63-1.19)
> 6.3	239	0.69 (0.58-0.83)	283	0.75 (0.63-0.89)	91	0.97 (0.71-1.34)
p for trend		<0.0001		0.0012		0.5830
Soluble fiber						
≤ 2.8	294	1.00 (ref.)	311	1.00 (ref.)	86	1.00 (ref.)
> 2.8 – ≤ 3.6	274	0.84 (0.71-1.00)	288	0.88 (0.75-1.04)	86	1.02 (0.75-1.39)
> 3.6 – ≤ 4.7	298	0.86 (0.72-1.02)	260	0.77 (0.64-0.92)	87	1.06 (0.77-1.46)
> 4.7	281	0.74 (0.61-0.88)	296	0.86 (0.72-1.03)	95	1.15 (0.83-1.59)
p for trend		0.0023		0.0494		0.3887
Dietary fiber from vegetables						
≤ 1.9	304	1.00 (ref.)	318	1.00 (ref.)	115	1.00 (ref.)
> 1.9 – ≤ 2.6	298	1.11 (0.94-1.31)	291	1.02 (0.86-1.20)	73	0.80 (0.58-1.08)
> 2.6 – ≤ 3.7	320	0.98 (0.83-1.16)	349	1.10 (0.94-1.29)	90	0.86 (0.64-1.16)
> 3.7	288	0.91 (0.77-1.09)	264	0.82 (0.69-0.98)	100	1.00 (0.75-1.35)
p for trend		0.1647		0.1054		0.9307
Dietary fiber from fruits						
≤ 1.3	284	1.00 (ref.)	309	1.00 (ref.)	83	1.00 (ref.)
> 1.3 – ≤ 2.5	349	1.04 (0.88-1.23)	308	0.92 (0.78-1.08)	101	1.13 (0.83-1.54)
> 2.5 – ≤ 4.2	261	0.78 (0.65-0.93)	287	0.85 (0.71-1.01)	94	1.16 (0.84-1.59)
> 4.2	316	0.91 (0.76-1.08)	318	0.92 (0.77-1.10)	100	1.21 (0.88-1.68)
p for trend		0.0406		0.2686		0.2577
Dietary fiber from legumes						
≤ 0.4	266	1.00 (ref.)	285	1.00 (ref.)	89	1.00 (ref.)
> 0.4 – ≤ 0.9	306	0.94 (0.80-1.12)	309	0.89 (0.75-1.05)	95	0.93 (0.68-1.25)
> 0.9 – ≤ 1.8	311	1.06 (0.89-1.26)	320	1.06 (0.89-1.26)	89	0.96 (0.70-1.33)
> 1.8	327	0.88 (0.72-1.07)	308	0.90 (0.75-1.10)	105	1.16 (0.83-1.62)
p for trend		0.4213		0.7332		0.4078
Dietary fiber from grains						

	GS AP		Non-GS AP		Non-GS RAP/SCP	
	No. Cases	HR§ (95% CI)	No. Cases	HR§ (95% CI)	No. Cases	HR§ (95% CI)
≤ 2.3	285	1.00 (ref.)	318	1.00 (ref.)	94	1.00 (ref.)
> 2.3 – ≤ 3.3	309	0.93 (0.79-1.11)	307	0.89 (0.75-1.05)	116	1.10 (0.82-1.46)
> 3.3 – ≤ 4.6	311	1.00 (0.85-1.19)	277	0.88 (0.74-1.04)	77	0.81 (0.59-1.12)
> 4.6	305	0.90 (0.76-1.07)	320	0.92 (0.78-1.09)	91	0.89 (0.65-1.21)
p for trend		0.3845		0.3839		0.1880
Vegetables						
≤ 109.8	282	1.00 (ref.)	309	1.00 (ref.)	100	1.00 (ref.)
> 109.8 – ≤ 150.9	295	1.00 (0.85-1.19)	292	0.97 (0.82-1.14)	80	0.87 (0.64-1.17)
> 150.9 – ≤ 203.7	296	0.98 (0.83-1.16)	297	0.99 (0.84-1.17)	80	0.89 (0.66-1.20)
> 203.7	274	0.85 (0.71-1.01)	257	0.85 (0.71-1.01)	94	1.05 (0.78-1.41)
p for trend		0.0582		0.1029		0.7652
Fruits including juice						
≤ 80.7	293	1.00 (ref.)	310	1.00 (ref.)	85	1.00 (ref.)
> 80.7 – ≤ 149.0	309	1.00 (0.85-1.18)	293	0.97 (0.82-1.14)	86	1.07 (0.78-1.45)
> 149.0 – ≤ 243.6	269	0.85 (0.72-1.01)	264	0.85 (0.72-1.01)	99	1.24 (0.92-1.68)
> 243.6	276	0.85 (0.72-1.02)	288	0.93 (0.78-1.10)	84	1.05 (0.76-1.46)
p for trend		0.0230		0.2078		0.5482
Legumes						
≤ 8.0	290	1.00 (ref.)	324	1.00 (ref.)	96	1.00 (ref.)
> 8.0 – ≤ 14.8	293	1.01 (0.86-1.20)	290	0.95 (0.81-1.12)	102	1.20 (0.89-1.60)
> 14.8 – ≤ 27.5	321	1.05 (0.89-1.25)	314	1.05 (0.89-1.24)	90	1.06 (0.78-1.44)
> 27.5	306	0.85 (0.71-1.02)	294	0.92 (0.77-1.11)	90	1.09 (0.78-1.52)
p for trend		0.1496		0.6707		0.7612

*All intakes are reported as g/1000 kcal/day. Models for dietary fiber from vegetables, fruits, legumes, and grains are mutually exclusive.

§HR adjusted for BMI, alcohol intake, diabetes, vigorous activity, education, smoking-pack years, and calories. Number of cases may not add up to the total cases in Table 1 due to missing values.

Table 4

Associations between intakes of coffee, caffeine, vitamin D and milk and pancreatitis

	GS AP		Non-GS AP		Non-GS RAP/SCP	
	No. Cases	**HR[§] (95% CI)**	**No. Cases**	**HR[§] (95% CI)**	**No. Cases**	**HR[§] (95% CI)**
Regular Coffee (cups/day)						
None	340	1.00 (ref.)	415	1.00 (ref.)	122	1.00 (ref.)
≤ 1	567	1.11 (0.96-1.27)	514	0.82 (0.72-0.94)	161	0.89 (0.70-1.13)
2-3	199	1.01 (0.84-1.21)	183	0.74 (0.62-0.89)	59	0.80 (0.58-1.11)
≥ 4	41	0.91 (0.65-1.28)	43	0.65 (0.47-0.90)	12	0.58 (0.31-1.08)
p for trend		0.9126		<0.0001		0.0500
Caffeine (mg/day)						
≤ 43.0	268	1.00 (ref.)	316	1.00 (ref.)	108	1.00 (ref.)
> 43.0 – ≤ 135.3	298	1.08 (0.92-1.28)	315	0.98 (0.83-1.15)	79	0.72 (0.53-0.96)
> 135.3 – ≤ 247.8	308	1.10 (0.93-1.31)	266	0.81 (0.69-0.96)	80	0.70 (0.52-0.95)
> 247.8	273	0.99 (0.83-1.18)	258	0.76 (0.64-0.91)	87	0.71 (0.53-0.97)
p for trend		0.9663		0.0004		0.0307
Vitamin D (IU/1000 kcal/day)						
≤ 35.2	287	1.00 (ref.)	262	1.00 (ref.)	83	1.00 (ref.)
> 35.2 – ≤ 57.2	329	1.07 (0.91-1.26)	274	1.00 (0.84-1.19)	93	1.16 (0.86-1.56)
> 57.2 – ≤ 87.3	264	0.84 (0.71-1.00)	312	1.12 (0.95-1.33)	87	1.08 (0.79-1.47)
> 87.3	267	0.81 (0.68-0.96)	307	1.07 (0.90-1.27)	91	1.05 (0.77-1.43)
p for trend		0.0015		0.2548		0.9138
Milk (g/1000 kcal/day)						
≤ 17.8	287	1.00 (ref.)	286	1.00 (ref.)	81	1.00 (ref.)
> 17.8 – ≤ 52.8	299	0.97 (0.82-1.14)	276	0.92 (0.78-1.09)	91	1.10 (0.81-1.49)
> 52.8 – ≤ 108.3	279	0.84 (0.71-1.00)	290	0.95 (0.80-1.12)	97	1.18 (0.87-1.59)
> 108.3	282	0.82 (0.69-0.97)	303	0.96 (0.81-1.14)	85	0.99 (0.72-1.36)
p for trend		0.0071		0.7645		0.9312

[§]HR adjusted for BMI, alcohol intake, diabetes, vigorous activity, education, years, and calories. Number of cases may not add up to the total cases in Table 1 due to missing values.