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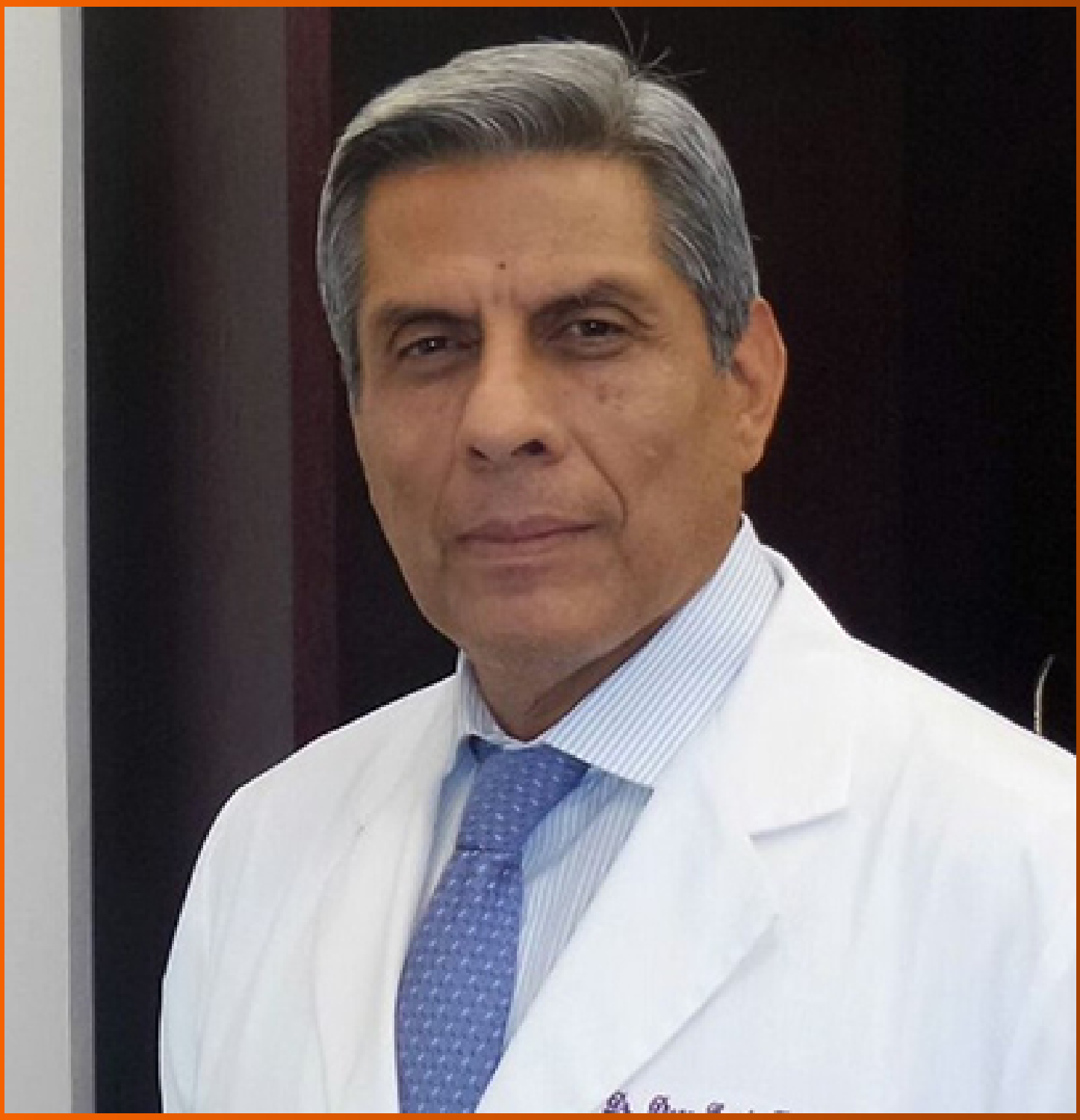

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ABOUT COVER

Editorial Board Member of *World Journal of Gastroenterology*, Dr. Diego Garcia-Compeán is a Distinguished Professor of Internal Medicine and Gastroenterology at Faculty of Medicine, Autonomous University of Nuevo Leon Mexico, where he received his degree in Medicine (1979) and completed postgraduate training in Internal Medicine (1982). He studied gastroenterology at the University of Montpellier, France (1985) and received a Master's in Medical Sciences with *cum laude* honors from the National Autonomous University of Mexico (1988). He is currently a member of the National Research System, level II, the Mexican Association of Gastroenterology, the Société Nationale Française de Gastroenterologie, the AGA, and the LAASL. His ongoing research interests involve NAFLD, eosinophilic esophagitis, liver cirrhosis, and VCE. He has published more than 75 papers in international journals, edited 3 books, and obtained national and international awards. (L-Editor: Filipodia)

AIMS AND SCOPE

The primary aim of *World Journal of Gastroenterology* (*WJG*, *World J Gastroenterol*) is to provide scholars and readers from various fields of gastroenterology and hepatology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online. *WJG* mainly publishes articles reporting research results and findings obtained in the field of gastroenterology and hepatology and covering a wide range of topics including gastroenterology, hepatology, gastrointestinal endoscopy, gastrointestinal surgery, gastrointestinal oncology, and pediatric gastroenterology.

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ORIGINAL ARTICLE

Prospective Study

Associations between serum uric acid and hepatobiliary-pancreatic cancer: A cohort study

Chong-Fei Huang, Jun-Jun Huang, Ning-Ning Mi, Yan-Yan Lin, Qiang-Sheng He, Ya-Wen Lu, Ping Yue, Bing Bai, Jin-Duo Zhang, Chao Zhang, Teng Cai, Wen-Kang Fu, Long Gao, Xun Li, Jin-Qiu Yuan, Wen-Bo Meng

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Author contributions: Huang CF, Huang JJ, Mi NN and Lin YY contributed equally to this work; Huang CF, Huang JJ, Mi NN, Lin YY, Meng WB and Yuan JQ designed the prospective study; Meng WB, Li X, Zhang C, Long Gao, Cai T, Huang CF, Huang JJ, Lin YY, Yue P, Fu WK and Bai B collected the data; Mi NN, He QS, Yuan JQ, Lu YW, Zhang JD, Zhang C and Long Gao analyzed the data; all authors participated in the writing and final approval of the manuscript.

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Abstract

BACKGROUND

statement: The UK Biobank has received ethical approval from the North West Multi-centre Research Ethics Committee, the England and Wales Patient Information Advisory Group and the Scottish Community Health Index Advisory Group.

Informed consent statement: All participants provided written informed consent prior to enrolment, and the analysis used anonymous data.

Conflict-of-interest statement: The authors have no conflicts of interest to declare.

Data sharing statement: All the data are available at: https://www.ukbiobank.ac.uk/.

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Uric acid is the end product of purine metabolism. Previous studies have found that serum uric acid (SUA) levels are associated with the total cancer risk. However, due to the dual effect of uric acid on cancer, the relationship between the SUA levels and most specific-site cancer remains unclear.

AIM

To investigate the associations between the SUA levels and incidence of hepatobiliary-pancreatic cancer.

METHODS

In this prospective cohort study, 444462 participants free of cancer from the UK Biobank were included. The SUA levels were measured at baseline, and the incidence of hepatobiliary-pancreatic cancer was determined by contacting the cancer registry. The hazard ratios (HRs) and 95% confidence intervals (CIs) between the SUA levels and hepatobiliary-pancreatic cancer were investigated using multiple adjusted Cox regression models adjusted for potential confounders.

RESULTS

In total, 920 participants developed liver, gallbladder, biliary tract or pancreatic cancer during a median of 6.6 yrs of follow-up. We found that the HR of pancreatic cancer in the highest SUA group was 1.77 (95%CI: 1.29-2.42) compared with that in the lowest group. After stratifying by gender, we further found that SUA was associated with an increased risk of pancreatic cancer only among the females (highest quartile *vs* lowest quartile HR 2.04, 95%CI: 1.35-3.08). Among the males, the SUA levels were positively associated with the gallbladder cancer risk (highest quartile *vs* lowest quartile HR 3.09, 95%CI: 1.28-7.46), but a U-shaped association with the liver cancer risk was observed (*P*-nonlinear = 0.03).

CONCLUSION

SUA is likely to have gender-specific effects on hepatobiliary-pancreatic cancer. High SUA levels are a risk factor for pancreatic cancer in females and gallbladder cancer in males. A U-shaped association with the liver cancer risk was identified.

Key Words: Uric acid; Liver neoplasms; Pancreatic neoplasms; Gallbladder neoplasms; Biliary tract neoplasms; Cohort studies

Core Tip: Serum uric acid has an effect on hepatobiliary-pancreatic cancer, specifically when stratified by gender. In males, high uric acid level is a risk factor for gallbladder cancer and has a U-shape association with liver cancer risk. In females, uric acid is positively associated with the risk of pancreatic cancer. In clinical and public health practice, management of either high or low uric acid levels may contribute to the prevention of hepatobiliary-pancreatic cancer.

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INTRODUCTION

Hepatobiliary-pancreatic (HBP) cancer includes liver cancer, biliary tract cancer, gallbladder cancer and pancreatic cancer[1-3]. The number of new cases of HBP cancer worldwide in 2018 was approximately 1.85 million, accounting for 10% of all newly diagnosed cancer cases and resulting in a great financial burden[4,5]. Due to the large

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number of HBP cancer cases, from the perspective of prevention[6,7], identifying high-risk populations has become an urgent public health issue[8-10].

Serum uric acid (SUA) is the final product of purine nucleotides that are ingested or endogenously synthesized and mainly metabolized by the liver[11]. Because of its function of inhibiting reactive oxygen species formation, SUA was considered a protective factor against cancer[12], and studies have indicated that elevated SUA was associated with low cancer mortality[13,14]. However, subsequent experiments revealed that SUA was associated with inflammatory mediators, which act as cancer-promoting factors[15,16]. A meta-analysis conducted in 2019 that included eight cohort studies investigating cancer incidence, and SUA suggested that high SUA levels increased the risk of all cancers[17].

However, few previously published studies have focused on the SUA levels and the incidence of cancer at specific sites, and none of these studies highlighted HBP cancer. Therefore, we conducted this study to evaluate the associations between SUA and the HBP cancer risk based on the UK Biobank cohort.

MATERIALS AND METHODS

Study design and population

The UK Biobank is a national and international health resource with over 500000 participants aged 40-69 years recruited from all over the United Kingdom from 2006-2010. More details of the UK Biobank are available elsewhere[18]. The UK Biobank has received ethical approval from the North West Multi-centre Research Ethics Committee, the England and Wales Patient Information Advisory Group and the Scottish Community Health Index Advisory Group. All participants provided written informed consent. In this analysis, we excluded 26868 participants with any cancer prior to recruitment (except for non-melanoma skin cancer 10th revision of the International Classification of Diseases C44) and 31197 participants with missing SUA data (Figure 1). Eventually, 444462 participants were included in the final analysis and were grouped by quartiles of SUA (Q1-Q4).

Data collection

The baseline characteristics were collected by self-completed touch-screen questionnaires, computer-assisted interviews and physical measurements. The data retrieved for the analysis included age, gender, education, ethnic group, family history of cancer, annual household income and lifestyle habits such as fruit and vegetable intake (more than five portions or not), alcohol consumption, smoking status, physical activity (categorized according to the standard International Physical Activity Questionnaire guidelines[19] as high, moderate or low) and body mass index [body mass index (BMI), calculated as weight divided by height squared, kg/m^2). Approximately 45 mL of blood and 9 mL of urine were collected to measure specific biomarkers by using the latest analytical methods in a dedicated facility in Stockport. The samples were stored separately for the subsequent detection and stored at -80 °C and -180 °C[20]. SUA was measured by a Beckman Coulter AU5800 (BC, United States) using enzymatic determination (Uricase PAP).

Diagnosis of cancer cases

Information regarding the cancer diagnoses in the UK Biobank is provided by the National Health Service (NHS) Digital and Public Health England for participants residing in England and Wales and the NHS Central Register for participants residing in Scotland. The general classification of the cancer cases was based on the 10th revision of the International Classification of Diseases codes. The primary outcomes in this study were liver cancer (C22), gallbladder cancer (C23), biliary tract cancer (C24) and pancreatic cancer (C25).

Statistical analysis

The baseline characteristics are presented as numbers (percentages) for the categorical variables and means (standard deviations) for the continuous variables. Cox regression models were used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) of the association between SUA and HBP cancer. The potential confounders were adjusted gradually in three models. In model 1, we adjusted for the general demographic characteristics (gender, age, education, ethnic group and family history of cancer). Then, we further adjusted for lifestyle factors (alcohol intake,

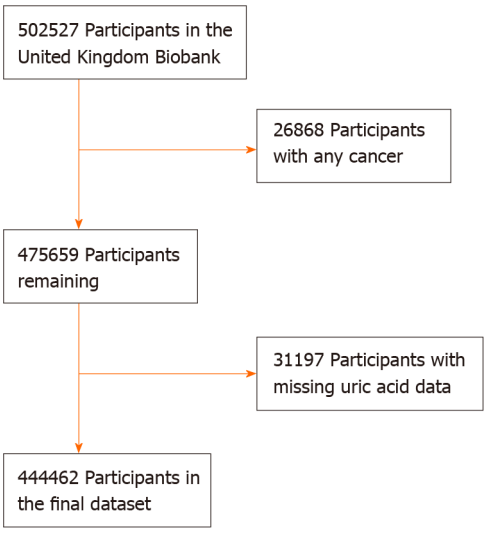

Figure 1 Flow chart of participant inclusion and exclusion.

smoking status, annual household income, physical activity, fruit and vegetable intake) in model 2. Because obesity is closely related to the SUA levels and cancer risk, in model 3, we adjusted for BMI separately in addition to the variables included in model 2. The potential nonlinear associations between the SUA levels and the HBP cancer risk were investigated by fitting restricted cubic splines in a fully adjusted Cox regression model. In addition, considering the large gender difference in the distribution of SUA, we also conducted a gender-stratified analysis.

A sensitivity analysis was performed to verify the stability of our results by excluding participants with less than 2 yrs of follow-up from the fully adjusted Cox regression models. All statistical analyses were conducted by using R software (version 3.5.0, R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

This study included 444462 participants (Tables 1 and 2). There were fewer males in the quartiles with higher SUA levels and fewer females in the quartiles with lower SUA levels. As the SUA level quartiles increased, the participants tended to be older, have a higher BMI, consume more alcohol, consume less fruit and vegetables and have fewer college or university degrees.

In total, 920 participants developed HBP cancer during a median of 6.6 yrs of follow-up. The risk of pancreatic cancer tended to increase with the SUA levels (adjusted HR per 1 mg/dL increase in SUA = 1.12, 95%CI: 1.04-1.21). In model 1, the HR of the pancreatic cancer risk was 1.91 (95%CI: 1.42-2.58) in the highest quartile (Q4) of SUA compared with the lowest quartile (Q1). After adjusting for potential confounders, the HR was gradually attenuated, but the association still existed in model 3. The risk of pancreatic cancer in the highest quartile of SUA increased by 77% compared with that in the lowest quartile (HR 1.77, 95%CI: 1.29-2.42, Table 3).

The stratified analysis results showed that SUA had different effects on HBP cancer between the males and females. In the male population, after fully adjusting for potential confounders, the risk of liver cancer decreased in the second quartile (HR 0.87, 95%CI: 0.57-1.34) and the third quartile (HR 0.61, 95%CI: 0.38-0.98) compared with that in the lowest quartile. However, in the highest quartile (HR 0.96, 95%CI: 0.63-1.46), the HR of liver cancer was increased compared with that in the third quartile (Figure 2A). In contrast to liver cancer, the risk of gallbladder cancer in the second quartile (HR 2.45, 95%CI: 0.90-6.70), the third quartile (HR 2.71, 95%CI: 1.05-6.98) and the highest quartile (HR 3.09, 95%CI: 1.28-7.46) were all higher than that in the lowest quartile (Figure 2D). The risk of biliary tract cancer and pancreatic cancer did not differ between the lowest and other quartiles (Figure 2B).

In the female population, no difference was found between the lowest quartile and the other quartiles of the SUA levels in gallbladder cancer and liver cancer. Regarding the biliary tract cancer risk, the HR of the highest quartile of SUA was 2.33 (95%CI:

Table 1 Baseline characteristic

Group	Q1	Q2	Q3	Q4
SUA level (mg/dL)	(1.50, 4.20)	(4.20, 5.09)	(5.09, 6.06)	(6.06, 17.90)
Number	111087	110975	111241	111159
Gender				
Male	99225 (89.3%)	73883 (66.6%)	44282 (39.8%)	21466 (19.3%)
Female	11862 (10.7%)	37092 (33.4%)	66959 (60.2%)	89693 (80.7%)
Mean age (SD)	55.30 (8.20)	56.90 (8.00)	57.50 (7.97)	57.70 (8.00)
White European	104975 (94.5%)	104411 (94.1%)	104447 (93.9%)	104475 (94.0%)
Current smokers	11629 (10.5%)	11 95 (10.6%)	12154 (10.9%)	11444 (10.3%)
Alcohol intake				
Over four times a week	40852 (36.8%)	45126 (40.7%)	49976 (44.9%)	57439 (51.7%)
Once or twice a week	29330 (26.4%)	29071 (26.2%)	28787 (25.9%)	27396 (24.6%)
One to three times a month	14577 (13.1%)	13324 (12.0%)	1 850 (10.7%)	9681 (8.7%)
Seldom or never	26102 (23.5%)	23203 (20.9%)	20363 (18.3%)	16388 (14.7%)
Fruit and vegetable intake				
Yes	47673 (42.9%)	44146 (39.8%)	40049 (36.0%)	35593 (32.0%)
No	63175 (56.9%)	66545 (60.0%)	70869 (63.7%)	75234 (67.7%)
Physical activity				
High	36219 (32.6%)	36706 (33.1%)	36948 (33.2%)	36029 (32.4%)
Moderate	37562 (33.8%)	36235 (32.7%)	36318 (32.6%)	36115 (32.5%)
Low	14838 (13.4%)	16003 (14.4%)	17162 (15.4%)	19457 (17.5%)
Annual household income				
Less than £18000	20748 (18.7%)	21456 (19.3%)	21341 (19.2%)	21536 (19.4%)
£18000 to £30999	23304 (21.0%)	24243 (21.8%)	24310 (21.9%)	24159 (21.7%)
£31000 to £51999	24672 (22.2%)	24624 (22.2%)	25270 (22.7%)	25168 (22.6%)
£52000 to £100000	19676 (17.7%)	18781 (16.9%)	19544 (17.6%)	20555 (18.5%)
Greater than £100000	5132 (4.6%)	4947 (4.5%)	5211 (4.7%)	5666 (5.1%)
College or University degree	38460 (34.6%)	36499 (32.9%)	35860 (32.2%)	33817 (30.4%)
Family history of cancer	38048 (34.3%)	38942 (35.1%)	39465 (35.5%)	39063 (35.1%)
Mean BMI, kg/m^2 (SD)	25.10 (4.01)	26.80 (4.45)	28.10 (4.62)	29.60 (4.82)

SUA: Serum uric acid; SD: Standard deviation; BMI: Body mass index; Q: Quartile.

1.14-4.76) compared with the lowest quartile in model 2 (Table 4). However, after additionally adjusting for BMI in model 3, the risk was attenuated (HR 1.65, 95%CI: 0.81-3.36). Regarding the pancreatic cancer risk, the risk increased by 1.33 times per 1 mg/dL SUA level in model 3 (HR 1.33, 95%CI: 1.21-1.47, Table 4). After an additional adjustment for potential confounders, the highest quartile still showed an increased risk compared with the lowest quartile (HR 2.04, 95%CI: 1.35-3.08, Figure 2C).

Figure 3 shows the evaluation of the potential nonlinear relationship with HBP cancer. A strong linear dose-response relationship was observed between the SUA levels and the risk of pancreatic cancer (*P*-nonlinear > 0.05, *P*-overall < 0.0001, Figure 3). After the stratification by genders, the SUA levels exhibited a linear dose-response relationship with the risk of pancreatic cancer in both the male and female populations, but the effect was much stronger in the females than in the males (*P*-interaction < 0.0001, Figure 4). The liver cancer risk showed a U-shaped relationship with the SUA levels (*P*-nonlinear < 0.05, *P*-overall < 0.0001, Figure 3); however, a nonlinear relationship with the risk of liver cancer was observed only in the males (*P*-

Table 2 Baseline characteristic stratified by gender

	Male				Female			
Group	Quartile 1	Quartile 2	Quartile 3	Quartile 4	Quartile 1	Quartile 2	Quartile 3	Quartile 4
SUA level (mg/dL)	(1.50, 5.13)	(5.13, 5.87)	(5.87, 6.69)	(6.69, 17.90)	(1.50, 3.77)	(3.77, 4.42)	(4.42, 5.18)	(5.18, 12.90)
Number	51349	51445	51364	51448	59639	59627	59872	59718
Mean age (SD)	56.90 (8.23)	56.90 (8.23)	57.00 (8.17)	57.30 (8.13)	54.60 (8.18)	56.00 (8.05)	57.20 (7.83)	58.90 (7.33)
White European	48082 (93.6%)	48342 (94.0%)	48405 (94.2%)	48480 (94.2%)	56435 (94.6%)	56437 (94.7%)	56340 (94.1%)	55787 (93.4%)
Current smokers	7983 (15.5%)	6579 (12.8%)	5816 (11.3%)	5377 (10.5%)	5759 (9.7%)	5412 (9.1%)	5138 (8.6%)	4958 (8.3%)
Alcohol intake								
Over four times a week	23146 (45.1%)	25543 (49.6%)	27432 (53.4%)	29611 (57.5%)	20964 (35.1%)	22423 (37.6%)	22866 (38.2%)	21408 (35.8%)
Once or twice a week	13636 (26.6%)	13770 (26.8%)	13308 (25.9%)	12478 (24.3%)	15822 (26.5%)	15714 (26.4%)	15444 (25.8%)	14412 (24.1%)
One to three times a month	5297 (10.3%)	4919 (9.6%)	4300 (8.4%)	3749 (7.3%)	8141 (13.7%)	7837 (13.1%)	7669 (12.8%)	7520 (12.6%)
Seldom or never	9124 (17.8%)	7098 (13.8%)	6203 (12.0%)	5500 (10.7%)	14598 (24.5%)	13546 (22.7%)	13761 (23.0%)	16226 (27.2%)
Fruit and vegetable intake								
Yes	16819 (32.8%)	16373 (31.8%)	15863 (30.9%)	15126 (29.4%)	26202 (43.9%)	26292 (44.1%)	25919 (43.3%)	24867 (41.6%)
No	34326 (66.8%)	34910 (67.9%)	35318 (68.8%)	36183 (70.3%)	33328 (55.9%)	33228 (55.7%)	33826 (56.5%)	34704 (58.1%)
Physical activity								
High	19424 (37.8%)	19002 (36.9%)	18382 (35.8%)	17317 (33.7%)	19204 (32.2%)	18936 (31.8%)	18096 (30.2%)	15541 (26.0%)
Low	7605 (14.8%)	7864 (15.3%)	8360 (16.3%)	9204 (17.9%)	7781 (13.0%)	8103 (13.6%)	8586 (14.3%)	9957 (16.7%)
Moderate	16226 (31.6%)	16580 (32.2%)	16858 (32.8%)	16777 (32.6%)	20402 (34.2%)	20063 (33.6%)	19842 (33.1%)	19482 (32.6%)
Annual household income								
Less than £18000	10135 (19.7%)	8851 (17.2%)	8622 (16.8%)	9477 (18.4%)	10830 (18.2%)	10982 (18.4%)	11999 (20.0%)	14185 (23.8%)
£18000 to £30999	11380 (22.2%)	11083 (21.5%)	11039 (21.5%)	10931 (21.2%)	12249 (20.5%)	12676 (21.3%)	13038 (21.8%)	13620 (22.8%)
£31000 to £51999	12024 (23.4%)	12537 (24.4%)	12538 (24.4%)	12138 (23.6%)	13368 (22.4%)	13137 (22.0%)	12663 (21.2%)	11329 (19.0%)
£52000 to £100000	9559 (18.6%)	10489 (20.4%)	10708 (20.8%)	10307 (20.0%)	10844 (18.2%)	10200 (17.1%)	9238 (15.4%)	7211 (12.1%)
Greater than £100000	2471 (4.8%)	2874 (5.6%)	3002 (5.8%)	2921 (5.7%)	2839 (4.8%)	2704 (4.5%)	2397 (4.0%)	1748 (2.9%)
College or university degree	18240 (35.5%)	18096 (35.2%)	17459 (34.0%)	15895 (30.9%)	21019 (35.2%)	20036 (33.6%)	18344 (30.6%)	15547 (26.0%)
Family history of cancer	17522 (34.1%)	17651 (34.3%)	17911 (34.9%)	17933 (34.9%)	20375 (34.2%)	20767 (34.8%)	21329 (35.6%)	22030 (36.9%)
Mean BMI, kg/m^2 (SD)	26.30 (3.90)	27.30 (3.87)	28.20 (3.99)	29.60 (4.41)	24.60 (3.82)	25.90 (4.29)	27.40 (4.82)	30.30 (5.79)

SUA: Serum uric acid; SD: Standard deviation; BMI: Body mass index.

nonlinear < 0.05, Figure 5). Additionally, regarding the SUA levels and the risk of gallbladder cancer and biliary tract cancer, a linear dose-response relationship was observed.

These results suggest that high SUA levels are associated with an increased risk of pancreatic cancer in females and gallbladder cancer in the males. Moreover, the risk of liver cancer showed a U-shaped association in the males as both too high and too low levels of SUA were associated with an increased risk. We did not observe sufficient evidence of an association between the SUA levels and biliary tract cancer.

In the sensitivity analysis, by excluding cases that were documented in the first 2 yrs, we did not observe major changes in the primary results (Tables 5 and 6).

DISCUSSION

As a very common metabolite, SUA has multiple effects on the human body, and high SUA levels have been considered harmful. Previous studies have found that elevated SUA levels are associated with gout, diabetes, hypertension, hyperlipidemia,

Table 3 Effect of serum uric acid on hepatobiliary-pancreatic cancer

Cancer	Group	Cases	Incidence[1]	HR (95%CI)		
				Model 1	Model 2	Model 3
Liver	Q1	42	5.76	1.00 (reference)	1.00 (reference)	1.00 (reference)
	Q2	62	8.45	1.08 (0.72-1.60)	1.08 (0.73-1.61)	1.00 (0.67-1.50)
	Q3	62	8.58	0.90 (0.59-1.36)	0.90 (0.59-1.36)	0.79 (0.52-1.21)
	Q4	95	13.12	1.20 (0.80-1.81)	1.18 (0.79-1.78)	0.98 (0.64-1.49)
	Estimated HR (per 1 mg/dL)			1.08 (0.97-1.19)	1.06 (0.96-1.17)	1.01 (0.91-1.13)
Gallbladder	Q1	13	1.78	1.00 (reference)	1.00 (reference)	1.00 (reference)
	Q2	15	2.05	1.02 (0.48-2.19)	1.01 (0.47-2.18)	0.98 (0.45-2.12)
	Q3	10	1.38	0.85 (0.37-1.97)	0.84 (0.36-1.93)	0.79 (0.33-1.86)
	Q4	18	2.49	1.52 (0.68-3.39)	1.45 (0.65-3.24)	1.32 (0.56-3.11)
	Estimated HR (per 1 mg/dL)			1.09 (0.87-1.35)	1.07 (0.86-1.33)	1.04 (0.82-1.31)
Biliary tract	Q1	11	1.51	1.00 (reference)	1.00 (reference)	1.00 (reference)
	Q2	19	2.59	1.36 (0.64-2.89)	1.37 (0.65-2.93)	1.32 (0.61-2.89)
	Q3	27	3.74	1.64 (0.78-3.47)	1.69 (0.80-3.58)	1.48 (0.68-3.22)
	Q4	17	2.35	0.94 (0.41-2.15)	0.99 (0.43-2.27)	0.75 (0.31-1.82)
	Estimated HR (per 1 mg/dL)			0.92 (0.76-1.13)	0.94 (0.77-1.14)	0.85 (0.69-1.05)
Pancreas	Q1	76	10.43	1.00 (reference)	1.00 (reference)	1.00 (reference)
	Q2	115	15.68	1.31 (0.97-1.75)	1.31 (0.98-1.76)	1.29 (0.96-1.73)
	Q3	155	21.45	1.68 (1.26-2.24)	1.69 (1.27-2.26)	1.61 (1.19-2.16)
	Q4	183	25.28	1.91 (1.42-2.58)	1.92 (1.43-2.59)	1.77 (1.29-2.42)
	Estimated HR (per 1 mg/dL)			1.15 (1.07-1.23)	1.15 (1.07-1.23)	1.12 (1.04-1.21)

Model 1 adjusted for gender, age, education, ethnic group and family history of cancer. Model 2 adjusted for gender, age, education, ethnic group, family history of cancer, alcohol intake, smoking status, annual household income, fruit and vegetable intake and physical activity. Model 3 additionally adjusted for body mass index based on model 2.

[1]Per 100000 person years. HR: Hazard ratio; CI: Confidence interval.

obesity[21-25] and cancer[26-28]. Kolonel *et al*[29] conducted a prospective cohort study including 7889 males and indicated that high SUA levels were associated with a high prostate cancer risk. Deng *et al*[30] included 8274 patients with type 2 diabetes from the Shanghai Diabetes Registry and found that in female diabetic patients, SUA was positively associated with the cancer risk. Another Mendelian randomization study analyzed 86210 individuals from the Copenhagen General Population Study and indicated that high SUA levels were associated with an increased cancer risk[31]. In our research, we also found a relationship between high SUA levels and an increased risk of pancreatic cancer in females and gallbladder cancer in males.

SUA has been found to be associated with inflammatory stress, which is closely related to the occurrence of cancer. Components of the inflammatory microenvironment, such as adiponectin, C-reactive protein, leptin and cyclooxygenase 2 (COX-2), which are closely related to SUA, were found to be associated with cancer development[15,32]. In addition, in our study, the SUA levels were positively correlated with pancreatic cancer and gallbladder cancer, and COX-2 was widely expressed in tumor tissues[33,34]. Xie *et al*[35] conducted an *in vitro* experiment examining the effect of COX-2 on the angiogenesis of pancreatic cancer cells and indicated that COX-2 was positively associated with the microvascular density, promoting pancreatic cancer cell growth. Celecoxib, a selective COX-2 inhibitor, was found to enhance the effect of chemotherapeutic drugs on pancreatic cancer and inhibit the proliferation of gallbladder cancer cells[36,37]. Ohtsubo *et al*[38] confirmed that SUA regulates the expression of COX-2 through XOR in *in vivo* and *in vitro* experiments, which may explain the association between SUA and cancer. Based on the evidence from previous

Table 4 Effect of uric acid on hepatobiliary-pancreatic cancer stratified by gender

Gender	Cancer	Group	Cases	Incidence[1]	HR (95%CI)		
					Model 1	Model 2	Model 3
Male	Liver	Quartile 1	44	13.12	1.00 (reference)	1.00 (reference)	1.00 (reference)
		Quartile 2	39	11.71	0.89 (0.58-1.37)	0.92 (0.60-1.42)	0.87 (0.57-1.34)
		Quartile 3	29	8.67	0.65 (0.41-1.05)	0.68 (0.42-1.08)	0.61 (0.38-0.98)
		Quartile 4	53	15.78	1.16 (0.78-1.73)	1.17 (0.78-1.75)	0.96 (0.63-1.46)
		Estimated HR (per 1 mg/dL)			1.07 (0.95-1.21)	1.07 (0.95-1.21)	1.01 (0.89-1.15)
	Gallbladder	Quartile 1	2	0.60	1.00 (reference)	1.00 (reference)	1.00 (reference)
		Quartile 2	5	1.50	2.48 (0.48-12.80)	2.54 (0.93-6.94)	2.45 (0.90-6.70)
		Quartile 3	6	1.79	2.91 (0.59-14.41)	2.93 (1.14-7.56)	2.71 (1.05-6.98)
		Quartile 4	8	2.38	3.67 (0.78-17.30)	3.56 (1.47-8.58)	3.09 (1.28-7.46)
		Estimated HR (per 1 mg/dL)			1.20 (0.86-1.67)	1.17 (0.85-1.60)	1.11 (0.81-1.53)
	Biliary tract	Quartile 1	13	3.88	1.00 (reference)	1.00 (reference)	1.00 (reference)
		Quartile 2	10	3.00	0.77 (0.34-1.76)	0.80 (0.35-1.84)	0.81 (0.35-1.88)
		Quartile 3	9	2.69	0.69 (0.30-1.62)	0.74 (0.32-1.75)	0.69 (0.29-1.67)
		Quartile 4	11	3.27	0.82 (0.37-1.83)	0.89 (0.39-2.00)	0.75 (0.32-1.75)
		Estimated HR (per 1 mg/dL)			0.82 (0.64-1.07)	0.85 (0.65-1.10)	0.80 (0.61-1.04)
	Pancreas	Quartile 1	68	20.28	1.00 (reference)	1.00 (reference)	1.00 (reference)
		Quartile 2	62	18.61	0.91 (0.65-1.29)	0.93 (0.66-1.32)	0.93 (0.66-1.32)
		Quartile 3	80	23.92	1.18 (0.85-1.62)	1.20 (0.87-1.66)	1.15 (0.83-1.60)
		Quartile 4	76	22.62	1.06 (0.77-1.48)	1.08 (0.77-1.50)	1.04 (0.74-1.47)
		Estimated HR (per 1 mg/dL)			1.02 (0.93-1.12)	1.02 (0.93-1.12)	1.01 (0.91-1.12)
Female	Liver	Quartile 1	20	5.06	1.00 (reference)	1.00 (reference)	1.00 (reference)
		Quartile 2	21	5.35	0.87 (0.47-1.64)	0.87 (0.47-1.64)	0.86 (0.46-1.62)
		Quartile 3	23	5.86	1.06 (0.59-1.91)	1.05 (0.58-1.90)	1.02 (0.56-1.87)
		Quartile 4	32	8.21	1.22 (0.69-2.15)	1.16 (0.65-2.05)	1.09 (0.59-2.02)
		Estimated HR (per 1 mg/dL)			1.10 (0.93-1.31)	1.08 (0.91-1.28)	1.06 (0.88-1.28)
	Gallbladder	Quartile 1	6	1.52	1.00 (reference)	1.00 (reference)	1.00 (reference)
		Quartile 2	10	2.55	1.47 (0.53-4.06)	1.49 (0.72-3.10)	1.47 (0.71-3.06)
		Quartile 3	10	2.55	1.31 (0.47-3.61)	1.30 (0.63-2.72)	1.27 (0.61-2.65)
		Quartile 4	9	2.31	1.02 (0.36-2.88)	0.99 (0.46-2.10)	0.94 (0.44-2.00)
		Estimated HR (per 1 mg/dL)			1.20 (0.86-1.67)	1.17 (0.85-1.60)	1.01 (0.75-1.35)
	Biliary tract	Quartile 1	4	1.01	1.00 (reference)	1.00 (reference)	1.00 (reference)
		Quartile 2	8	2.04	1.77 (0.53-5.88)	1.78 (0.80-3.97)	1.66 (0.74-3.71)
		Quartile 3	6	1.53	1.19 (0.33-4.22)	1.17 (0.48-2.85)	0.98 (0.40-2.39)
		Quartile 4	13	3.34	2.24 (0.72-6.94)	2.33 (1.14-4.76)	1.65 (0.81-3.36)
		Estimated HR (per 1 mg/dL)			0.82 (0.64-1.07)	0.85 (0.65-1.1)	1.09 (0.81-1.48)
	Pancreas	Quartile 1	35	8.86	1.00 (reference)	1.00 (reference)	1.00 (reference)
		Quartile 2	36	9.17	0.93 (0.58-1.48)	0.93 (0.58-1.47)	0.91 (0.57-1.44)
		Quartile 3	64	16.29	1.51 (1.00-2.28)	1.50 (0.99-2.27)	1.43 (0.94-2.18)
		Quartile 4	108	27.71	2.27 (1.54-3.34)	2.25 (1.53-3.31)	2.04 (1.35-3.08)

Estimated HR (per 1 mg/dL)	1.02 (0.93-1.12)	1.02 (0.93-1.12)	1.33 (1.21-1.47)

Model 1 adjusted for age, education, ethnic group and family history of cancer. Model 2 adjusted for age, education, ethnic group, family history of cancer, alcohol intake, smoking status, annual household income, fruit and vegetable intake and physical activity. Model 3 additionally adjusted for body mass index based on model 2.
[1]Per 100000 person years. HR: Hazard ratio; CI: Confidence interval.

Table 5 Sensitivity analysis

Cancer	Group	HR (95%CI)		
		Model 1	Model 2	Model 3
Liver	Quartile 1	1.00 (reference)	1.00 (reference)	1.00 (reference)
	Quartile 2	1.00 (0.64-1.55)	1.01 (0.65-1.57)	0.92 (0.59-1.43)
	Quartile 3	0.78 (0.49-1.24)	0.79 (0.50-1.25)	0.68 (0.42-1.08)
	Quartile 4	1.04 (0.66-1.63)	1.04 (0.66-1.63)	0.82 (0.51-1.31)
Gallbladder	Quartile 1	1.00 (reference)	1.00 (reference)	1.00 (reference)
	Quartile 2	1.68 (0.66-4.28)	1.71 (0.67-4.36)	1.63 (0.63-4.21)
	Quartile 3	1.41 (0.51-3.89)	1.42 (0.52-3.93)	1.31 (0.46-3.72)
	Quartile 4	2.71 (1.02-7.21)	2.72 (1.03-7.23)	2.40 (0.85-6.80)
Biliary tract	Quartile 1	1.00 (reference)	1.00 (reference)	1.00 (reference)
	Quartile 2	1.09 (0.48-2.47)	1.10 (0.49-2.51)	1.12 (0.48-2.61)
	Quartile 3	1.10 (0.48-2.50)	1.14 (0.50-2.60)	1.08 (0.46-2.55)
	Quartile 4	0.75 (0.31-1.82)	0.79 (0.32-1.93)	0.68 (0.26-1.75)
Pancreas	Quartile 1	1.00 (reference)	1.00 (reference)	1.00 (reference)
	Quartile 2	1.26 (0.90-1.76)	1.26 (0.90-1.77)	1.25 (0.89-1.76)
	Quartile 3	1.76 (1.27-2.44)	1.77 (1.28-2.46)	1.71 (1.22-2.40)
	Quartile 4	2.09 (1.49-2.92)	2.11 (1.51-2.95)	1.96 (1.38-2.80)

Model 1 adjusted for genders, age, education, ethnic group and family history of cancer. Model 2 adjusted for genders, age, education, ethnic group, family history of cancer, alcohol intake, smoking status, annual household income, fruit and vegetable intake and physical activity. Model 3 additionally adjusted for body mass index based on model 2. Participants with less than 2 yrs of follow-up were excluded. HR: Hazard ratio; CI: Confidence interval.

epidemiological and experimental studies along with our findings, high SUA levels are likely to lead to an increased risk of cancer in various sites, suggesting that we should pay attention to reducing the SUA levels to reduce the risk of cancer.

Although many studies have shown that high SUA levels are a risk factor for cancer, some evidence suggests that the SUA levels should not be too low. Ames *et al*[12]. first proposed the hypothesis that SUA might act as a protective factor against cancer due to its antioxidant function and its function as a scavenger of singlet oxygen and free radicals. Some epidemiological studies also supported this hypothesis. Tilman *et al*[39] conducted a population-based study of endogenous antioxidants, including albumin, bilirubin and SUA, and indicated that a high SUA level was associated with a low risk of breast cancer and low mortality of all cancers. Patients with oral cancer and lung cancer also had lower SUA levels[40,41]. The results of a cohort study confirmed that low SUA levels were associated with lung cancer[42]. In our study, we found that as the SUA levels increased, the risk of liver cancer first exhibited a downward trend. Male participants in the third quartile had a 39% decreased risk of liver cancer (HR 0.61, 95%CI: 0.38-0.98) compared with those in the lowest quartile, possibly due to the protective function of SUA. However, as the SUA levels further increased, the risk of liver cancer also increased. In the highest quartile, the risk of liver cancer was notably higher than the risk in the third quartile, revealing a U-shaped relationship. Strasak *et al*[43] conducted a population-based study involving Austrian men and suggested a J-shaped effect of SUA on the risk of overall cancer incidence, which is similar to our results in liver cancer, indicating that SUA within a proper range is better in the

Table 6 Sensitivity analysis stratified by gender

Gender	Cancer	Group	HR (95%CI)		
			Model 1	Model 2	Model 3
Male	Liver	Quartile 1	1.00 (reference)	1.00 (reference)	1.00 (reference)
		Quartile 2	0.88 (0.55-1.40)	0.92 (0.57-1.46)	0.86 (0.54-1.38)
		Quartile 3	0.60 (0.36-1.01)	0.62 (0.37-1.05)	0.56 (0.33-0.94)
		Quartile 4	0.99 (0.63-1.55)	0.99 (0.63-1.56)	0.81 (0.51-1.29)
	Gallbladder	Quartile 1	1.00 (reference)	1.00 (reference)	1.00 (reference)
		Quartile 2	3.04 (0.32-29.21)	3.20 (0.90-11.35)	3.01 (0.85-10.67)
		Quartile 3	4.92 (0.57-42.13)	5.22 (1.78-15.28)	4.58 (1.57-13.41)
		Quartile 4	5.52 (0.66-45.96)	5.85 (2.08-16.43)	4.64 (1.65-13.03)
	Biliary tract	Quartile 1	1.00 (reference)	1.00 (reference)	1.00 (reference)
		Quartile 2	0.83 (0.34-1.99)	0.87 (0.36-2.10)	0.88 (0.36-2.17)
		Quartile 3	0.82 (0.34-1.97)	0.88 (0.36-2.15)	0.83 (0.33-2.06)
		Quartile 4	0.70 (0.28-1.73)	0.77 (0.30-1.93)	0.64 (0.24-1.68)
	Pancreas	Quartile 1	1.00 (reference)	1.00 (reference)	1.00 (reference)
		Quartile 2	1.04 (0.70-1.55)	1.07 (0.72-1.59)	1.06 (0.71-1.59)
		Quartile 3	1.37 (0.95-1.99)	1.41 (0.97-2.04)	1.33 (0.91-1.95)
		Quartile 4	1.15 (0.78-1.69)	1.17 (0.79-1.73)	1.11 (0.74-1.66)
Female	Liver	Quartile 1	1.00 (reference)	1.00 (reference)	1.00 (reference)
		Quartile 2	0.91 (0.45-1.81)	0.92 (0.46-1.85)	0.89 (0.44-1.78)
		Quartile 3	0.98 (0.50-1.92)	1.00 (0.51-1.95)	0.92 (0.47-1.83)
		Quartile 4	1.05 (0.55-2.00)	1.02 (0.53-1.96)	0.88 (0.43-1.76)
	Gallbladder	Quartile 1	1.00 (reference)	1.00 (reference)	1.00 (reference)
		Quartile 2	2.06 (0.53-7.98)	2.13 (0.55-8.24)	2.11 (0.54-8.20)
		Quartile 3	2.38 (0.64-8.81)	2.47 (0.66-9.15)	2.42 (0.64-9.15)
		Quartile 4	2.08 (0.56-7.74)	2.10 (0.56-7.85)	2.02 (0.51-8.08)
	Biliary tract	Quartile 1	1.00 (reference)	1.00 (reference)	1.00 (reference)
		Quartile 2	1.56 (0.46-5.33)	1.56 (0.45-5.33)	1.48 (0.43-5.09)
		Quartile 3	0.80 (0.20-3.22)	0.80 (0.20-3.23)	0.72 (0.18-2.97)
		Quartile 4	1.23 (0.36-4.26)	1.29 (0.37-4.47)	1.04 (0.27-3.96)
	Pancreas	Quartile 1	1.00 (reference)	1.00 (reference)	1.00 (reference)
		Quartile 2	0.78 (0.47-1.32)	0.78 (0.46-1.31)	0.77 (0.46-1.29)
		Quartile 3	1.21 (0.77-1.92)	1.20 (0.76-1.90)	1.16 (0.73-1.85)
		Quartile 4	2.07 (1.37-3.13)	2.05 (1.35-3.10)	1.93 (1.24-3.01)

Model 1 adjusted for age, education, ethnic group and family history of cancer. Model 2 adjusted for age, education, ethnic group, family history of cancer, alcohol intake, smoking status, annual household income, fruit and vegetable intake and physical activity. Model 3 additionally adjusted for body mass index based on model 2. Participants with less than 2 yrs of follow-up were excluded. HR: Hazard ratio; CI: Confidence interval.

context of liver cancer, and too low or too high levels of SUA represent a risk factor for liver cancer. Similarly, COX-2 is overexpressed during the development of liver cancer and tumor tissues, while normal liver tissues scarcely express COX-2[44,45]. Chen *et al*[46] showed that COX-2 was a leading factor related to liver cancer in a spontaneous liver cancer mouse model that overexpressed COX-2 specifically in the liver. As the SUA levels increase, the cancer-promoting effect of COX-2 overexpression may be stronger, leading to the U-shaped association between SUA and liver cancer.

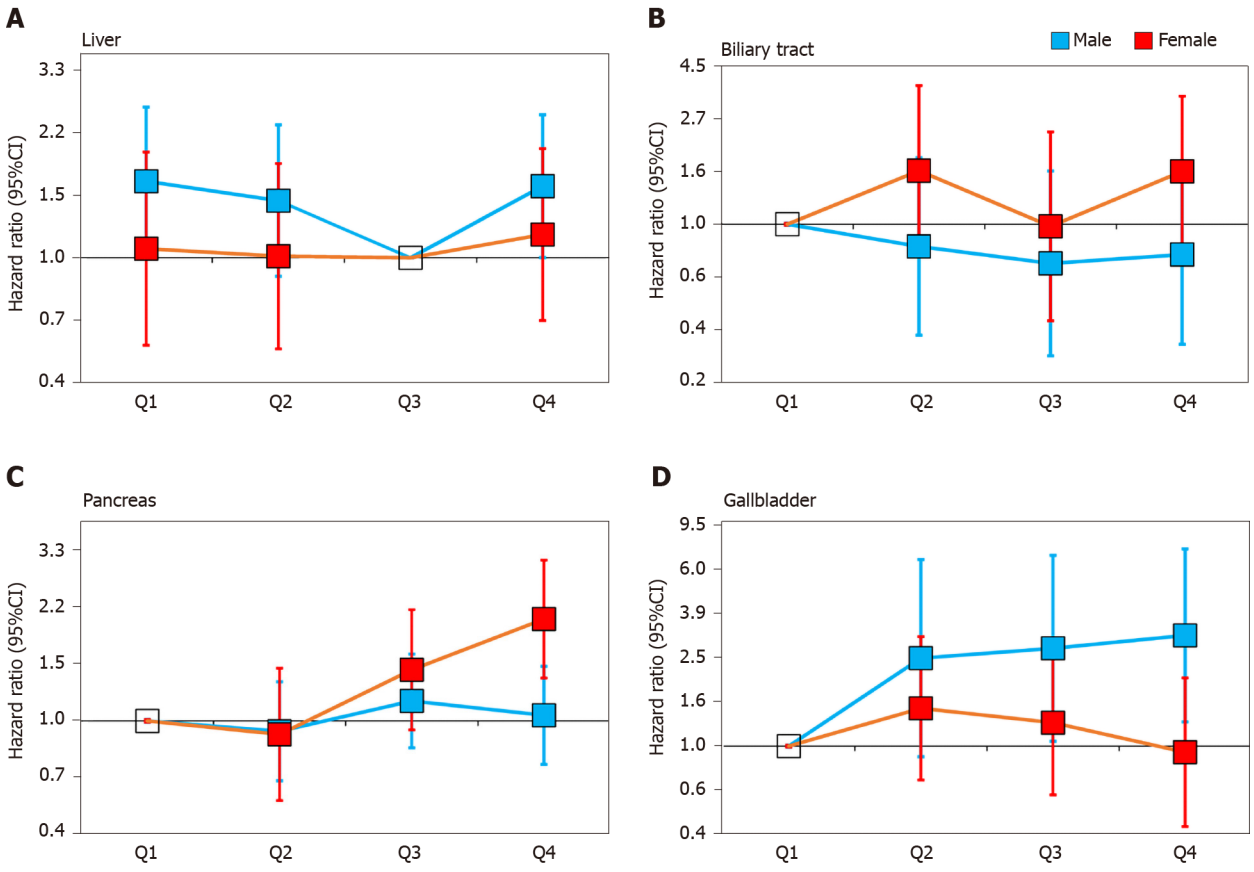

Figure 2 Associations between uric acid and hepatobiliary-pancreatic cancer stratified by gender. Adjusted for age, education, ethnic, family history of cancer, alcohol intake, smoking status, annual household income, fruit and vegetable intake and physical activity and body mass index. A: Liver; B: Biliary tract; C: Pancreas; D: Gallbladder. CI: Confidence interval.

In the gender stratified analysis, we found that only gallbladder cancer and liver cancer were associated with SUA in males, and that pancreatic cancer was related to SUA in females. This finding might be related to the reduced number of cases after the stratification as the statistical power was insufficient. In addition, we found that the risk associated with SUA in biliary tract, gallbladder and liver cancer in the female participants was generally higher than that in the male participants. Similar results were found in previous studies. A Chinese cohort study found that high SUA levels were associated with cancer risk in diabetic female patients[30]. Yan *et al*[47] conducted a systematic review and suggested that high SUA levels were associated with a high cancer risk, especially among females. Further analysis suggested that SUA and gender had an interactive effect on pancreatic cancer because sex hormones may lead to different sensitivity to SUA. More research is still required to reveal such gender differences.

To the best of our knowledge, this study is the first to focus on the association between SUA and HBP cancer. The main strength of our research is the large sample size. We included over 0.44 million participants in this analysis, allowing us to discover the relationship between the SUA levels and HBP cancer at multiple levels. Additionally, the UK Biobank comprehensively collected data related to established HBP cancer risk factors, allowing us to sufficiently control for potential confounders. We also investigated the potential nonlinear relationship, which provided insight into the carcinogenicity of SUA and contributes to individualized cancer prevention.

This study has limitations. First, as an observational study, we cannot confirm the causal-relationship between SUA and HBP cancer. Second, due to the limited number of cases, we were unable to conduct further stratified analyses of some variables. Third, in the UK Biobank, most included people were white Europeans, and the role of SUA in other races is unclear. More research is needed to compensate for the above limitations.

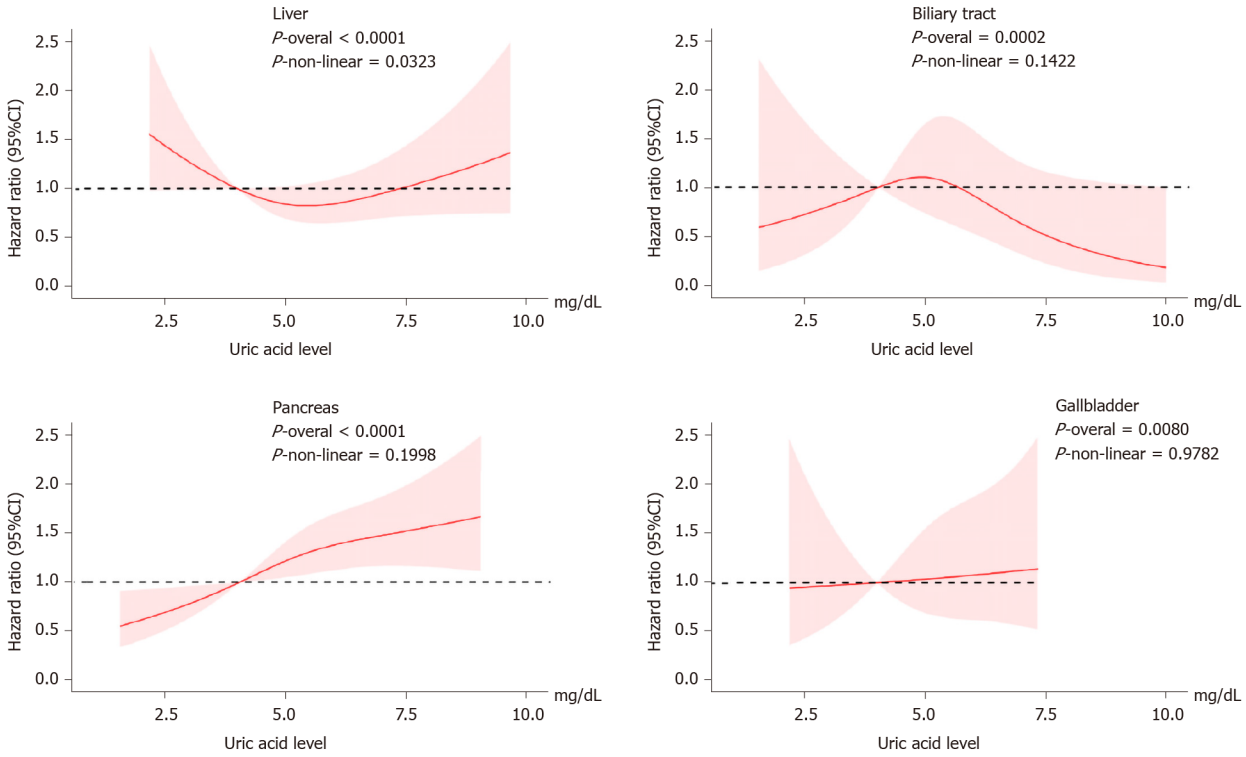

Figure 3 Dose response of uric acid and hepatobiliary-pancreatic cancer risk. Adjusted for genders, age, education, ethnic, family history of cancer, alcohol intake, smoking status, annual household income, fruit and vegetable intake and physical activity and body mass index. The reference uric acid level for these plots (with hazard ratio fixed as 1.0) was 4.0 mg/dL. CI: Confidence interval.

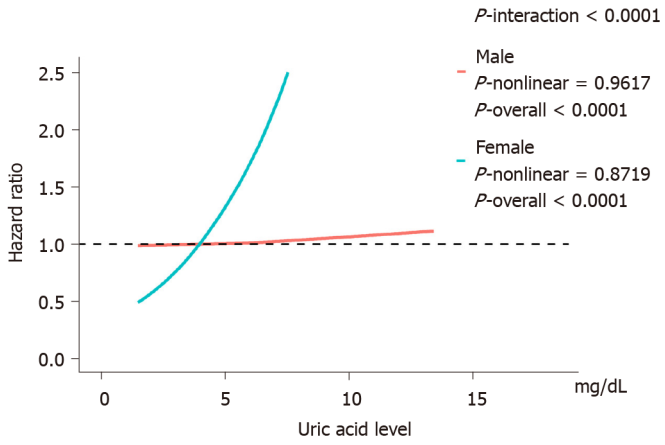

Figure 4 Association between uric acid level and pancreatic cancer with effect modification by gender. Adjusted for age, education, ethnic, family history of cancer, alcohol intake, smoking status, annual household income, fruit and vegetable intake and physical activity and body mass index. The reference uric acid level for these plots (with hazard ratio fixed as 1.0) was 4.0 mg/dL.

CONCLUSION

In conclusion, SUA is likely to have gender-specific effects on HBP cancer. High SUA levels represent a risk factor for gallbladder cancer in males and have a strong effect on pancreatic cancer in females. SUA levels that are too high or too low are associated with an increased risk of liver cancer in males. In clinical and public health practice, the management of either too high or too low SUA levels may contribute to the prevention of HBP cancer. Future research is required to confirm our conclusion and investigate the mechanisms underlying these associations.

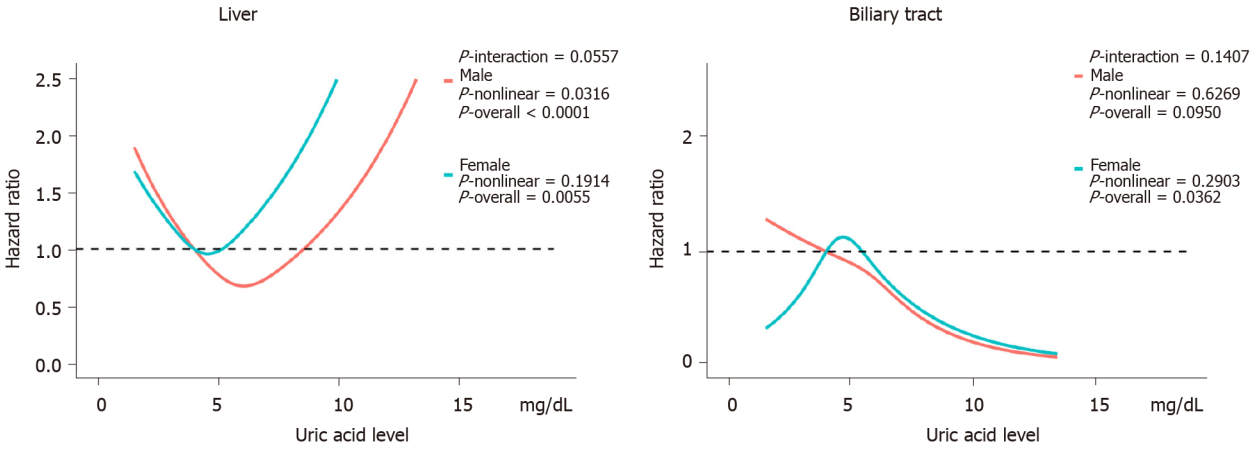

Figure 5 The effect of uric acid on hepatobiliary cancer stratified by gender. Adjusted for age, education, ethnic, family history of cancer, alcohol intake, smoking status, annual household income, fruit and vegetable intake and physical activity and body mass index. The reference uric acid level for these plots (with hazard ratio fixed as 1.0) was 4.0 mg/dL.

ARTICLE HIGHLIGHTS

Research background

In 2018, new cases of hepatobiliary-pancreatic (HBP) cancer reached 1.85 million and identifying high-risk populations has become an urgent public health issue. As one of the important metabolites of the human body, serum uric acid (SUA) is considered to be related to cancer risk, but there is controversy about its role in specific cancers.

Research motivation

Because of the dual effect of SUA on cancer risk, the associations between SUA levels and the HBP cancer risk remain unclear.

Research objectives

To evaluate the associations between SUA levels and incidence of hepatobiliary-pancreatic cancer based on the UK Biobank cohort and to investigate the gender differences.

Research methods

This is a prospective cohort study from the UK Biobank. We estimated the hazard ratios and 95% confidence intervals between SUA levels and hepatobiliary-pancreatic cancer by using multiple adjusted Cox regression models adjusted for potential confounders. In addition, we also conducted a sensitivity analysis to verify the stability of our results.

Research results

We included 444462 participants free of cancer. With a median of 6.6 yrs of follow-up, 920 participants developed liver, gallbladder, biliary tract or pancreatic cancer. The risk of pancreatic cancer increases with the SUA levels; however, after the gender-stratified analysis, the association only occurred among the females. Both too high and too low SUA levels are the risk factors of liver cancer among the males. For gallbladder cancer, the positive association with SUA levels was identified among the males. Regarding biliary tract cancer, there is not sufficient evidence for biliary tract cancer and SUA levels.

Research conclusions

SUA is likely to have gender-specific effects on HBP cancer. In clinical and public health practice, controlling SUA levels in an appropriate range may help prevent HBP cancer.

Research perspectives

In the future, more research is needed to investigate the association between the SUA levels and other specific-site cancer risk and the underlying mechanism.

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