Clinics and Research in Hepatology and Gastroenterology 49 (2025) 102616

Contents lists available at ScienceDirect

Clinics and Research in Hepatology and Gastroenterology

journal homepage: www.elsevier.com/locate/clinre

Original article

Analgesics use and risk of pancreatitis: Result from the UK Biobank

Jiayi Wang [a,#], Wanxin Long [a,#], Zehong Qi [b], Yangjie Liao [c], Jingbo Li [a,*]

[a] Department of Gastroenterology, The Third Xiangya Hospital, Central South University, Changsha 410013, China
[b] Department of Pathophysiology, School of Basic Medicine Science, Central South University, Changsha 410078, China
[c] Department of Gastroenterology, Changde Hospital, Xiangya School of Medicine, Central South University (The first people's hospital of Changde city), Changde 415000, China

ARTICLE INFO

Keywords:
Prospective cohort study
Pancreatitis
Analgesics
UK Biobank

ABSTRACT

Background: Pancreatitis, an inflammatory pancreatic disorder, arises from various etiologies including alcohol, tobacco, and drug use. Although the initiation of pancreatitis has been strongly linked to several medications, the association between analgesic use and pancreatitis risk remains ambiguous in population-based studies.
Methods: This prospective cohort study involved 324,982 participants from the UK Biobank. Multivariable-adjusted Cox proportional hazards models were conducted to evaluate the longitudinal association between incident pancreatitis risk and analgesics use, encompassing opioids, non-steroidal anti-inflammatory drugs (NSAIDs), paracetamol, antimigraine preparations, and the mix. Subgroup and sensitivity analyses were conducted to assess the potential effects of baseline factors.
Results: Over a median follow-up of 13.70 years, 2303 cases of pancreatitis were identified. In the fully adjusted model, analgesics utilization increased the risk of pancreatitis (HR 1.13, 95 % CI 1.04–1.23), acute pancreatitis (AP) (HR 1.11, 95 % CI 1.01–1.22), and chronic pancreatitis (CP) (HR 1.25, 95 % CI 1.00–1.56) (All the above $p < 0.05$). Furthermore, participants who used opioids presented the highest risk of pancreatitis (HR 1.85, 95 % CI 1.49–2.31, $p < 0.001$), and the mixed group (HR 1.35, 95 % CI 1.21–1.51, $p < 0.001$) followed. Compared to the non-analgesics group, the risk of both AP and CP also increased in the opioids and the mixed group. Subgroup analysis indicated that the impact of analgesics utilization on the pancreatitis risk may vary with certain covariates, such as age, cholelithiasis, etc. (p-interaction <0.05).
Conclusion: In this large population-based prospective cohort, analgesics utilization, particularly opioids and mixed analgesics, was linked to an increased risk of pancreatitis.

1. Introduction

Pancreatitis is a multifactorial, progressive inflammatory condition of the pancreas, pathologically classified into acute pancreatitis (AP) and chronic pancreatitis (CP) based on their distinct clinical and pathological courses. Globally, the incidence of AP is approximately 33.74 cases per 100,000 individuals annually, while CP has an incidence rate of 9.62 cases per 100,000 [1]. Due to its considerable morbidity, mortality, and socioeconomic burden [2], pancreatitis is increasingly recognized as a critical public health issue. Despite advancements in medical technology, the prevention of pancreatitis remains challenging due to the complex etiologies involved.

Presently, identified risk factors for pancreatitis include gallstones, alcohol consumption, tobacco use, autoimmune diseases, drugs, etc. [3–5]. While the first three have been traditionally acknowledged as primary etiologies, there is growing evidence suggesting that medications represent modifiable risk factors. Numerous studies have demonstrated that specific drugs, including antineoplastic agents, antibiotics, and analgesics, contribute to pancreatitis development [6–9].

Analgesics, as a common therapeutic drug, can be categorized into four types according to the Anatomical Therapeutic Chemical Classification System [10]: opioids, non-steroidal anti-inflammatory drugs (NSAIDs), paracetamol (also known as acetaminophen), and antimigraine preparations. A prospective multicenter cohort study has indicated that opioid utilization exacerbates the severity of AP [11]. It has been reported that an overdose of paracetamol can induce pancreatitis [12]. A series of reviews have identified certain analgesics, such as codeine and naproxen, as being linked to an increased risk of

* Corresponding author.
E-mail address: jingboli@csu.edu.cn (J. Li).
# Jiayi Wang and Wanxin Long are contributed equally to this work.

https://doi.org/10.1016/j.clinre.2025.102616

Available online 20 May 2025

pancreatitis [7,8,13]. However, there is a paucity of large prospective cohort studies investigating the relationship between analgesics utilization and the onset of pancreatitis.

In order to provide a novel insight into the prevention of pancreatitis, we conducted a population-based prospective cohort study utilizing data from the UK Biobank. This study aimed to investigate the association between analgesics utilization and the incidence of pancreatitis and to further explore the relationship between different types of analgesics and pancreatitis.

2. Methods

2.1. Study population

The UK Biobank (https://www.ukbiobank.ac.uk/) is a large prospective cohort study comprising over 500,000 participants aged 40 to 69 years recruited between 2006 and 2010 [14]. It was approved by the National Health Service (NHS) North West Multi-Center Research Ethics Committee.

In this study, 502,364 participants were initially recruited from the UK Biobank. After excluding participants with incomplete medication information ($n = 138,477$), diagnosed with AP and CP at the same time ($n = 521$), diagnosed with pancreatitis at recruitment ($n = 933$), with prevalent cancer at recruitment (according to NHS cancer register) ($n = 37,451$), a total of 324,982 individuals were finally enrolled in this study (Fig. 1). These individuals were tracked until the occurrence of pancreatitis diagnosis, death, or the last follow-up, whichever came first.

2.2. Assessment of exposure

The type and number of medications taken were obtained through a verbal interview by a trained nurse in the UK Biobank (code 20003). Participants entered regular prescription medications in the questionnaire under a nurse's guidance, while short-term drugs, over-the-counter medications, doses, and formulations were not recorded. Detailed information regarding medication codes is available in Table S8. We initially stratified the population into dichotomous variables based on analgesics use (non-analgesics utilization group and analgesics utilization group). Participants who reported analgesics use were further divided into four single-drug use groups if they exclusively used one type of analgesics (the opioids group, the NSAIDs group, the paracetamol group, and the antimigraine preparations group) according to the Anatomical Therapeutic Chemical Classification System [10], whereas if participants used two or more types of analgesics, they were classified as a mixed group.

2.3. Ascertainment of pancreatitis

Pancreatitis was identified using the International Classification of Disease 9th and 10th Revisions (ICD-9 and ICD-10), as well as self-reported pancreatitis (code 1165) [15]. This classification encompassed various forms of pancreatitis, including AP and CP. Detailed information is available in Table S1.

2.4. Covariates

In accordance with the extant literature and prior research findings, a set of covariates was incorporated into this analysis [1,3,5,16–18]. Participants provided sociodemographic, lifestyle, and health-related information through touchscreen questionnaires and verbal interviews with a trained nurse. The sociodemographic characteristics included age (continuous), gender (female or male), ethnicity (white or non-white), education level (college or non-college), body mass index (BMI, continuous in kg/m^2), and the Townsend deprivation index (TDI, continuous). The TDI score served as a surrogate measure for material socioeconomic deprivation [19]. Lifestyle factors included alcohol consumption (never or current), smoking status (never or ever), and physical activity levels (low, moderate, or high). Diseases associated with pancreatitis included cholelithiasis (yes or no) and diabetes (yes or no). Factors related to analgesic use included chronic pain and pain site. Chronic pain was operationally defined as pain persisting for at least three months, affecting at least one site or the entire body [20]. The number of pain sites was categorized into eight levels, ranging from "0" to "7 or all over". Detailed information on the covariates is available in Table S2.

2.5. Statistical analysis

We conducted comparative analyses of the baseline characteristics between participants in the non-analgesics utilization group and the analgesics utilization group, and further compared the differences among participants across different types of analgesics utilization. Baseline characteristics were reported as means with standard deviations for continuous variables and as numbers with percentages for categorical variables. Missing data of the covariates were handled as follows: median imputation was applied to continuous variables, while categorical variables with < 3 % missingness were imputed using the maximum group. Categorical variables with ≥ 3 % missingness retained 'missing' as a distinct category.

The Cox proportional hazards model was utilized to evaluate the association between analgesics utilization and the risk of pancreatitis. Model 1 was adjusted for age, sex, ethnicity, education, and TDI. Model 2 further adjusted for alcohol consumption, smoking status, and physical activity based on Model 1. Model 3, built upon Model 2, additionally incorporated adjustments for cholelithiasis and diabetes. Subsequently, to test effect modification of these covariates, subgroup analyses were conducted within Model 3 and fitted interaction terms between analgesic use and the aforementioned covariates. Additionally, we performed sensitivity analyses using the E-value approach to investigate the potential impact of unmeasured confounders on the association between analgesics utilization and the risk of pancreatitis [21]. This method evaluates the minimum strength of association that an unmeasured cofounder would need to have with both analgesics utilization and the risk of pancreatitis to account for the statistically significant effect observed in our study. The calculations were based on the hazard ratio (HR) derived from Model 3.

All statistical tests were two-tailed, with statistical significance defined as $p < 0.05$. Statistical analyses were conducted using R software (version 4.3.3).

3. Results

3.1. Baseline characteristics of the study population

Within the study cohort, 144,322 individuals (44.4 %) were included in the no analgesics group, while 180,660 (55.6 %) were in the analgesics group. Compared to the non-analgesics group, participants in the analgesics group were more likely to be male, previous or current smokers, and to have higher socioeconomic deprivation, BMI, diabetes, cholelithiasis, chronic pain incidence, a greater number of pain sites, and less physical activity. Conversely, the non-analgesics group had a higher proportion of current drinkers, participants of white ethnicity, and participants with a college degree (Table 1).

Among the analgesic groups, the largest number of participants utilized NSAIDs ($n = 75,022$), followed by those using mixed analgesics, paracetamol, opioids, and antimigraine preparations. Compared with other groups, participants in the opioid group were more likely to be older, previous or current smokers, more socioeconomically deprived, cholelithiasis patients, with higher BMI, less physically active, and a higher incidence of chronic pain. Detailed information is provided in Table S3.

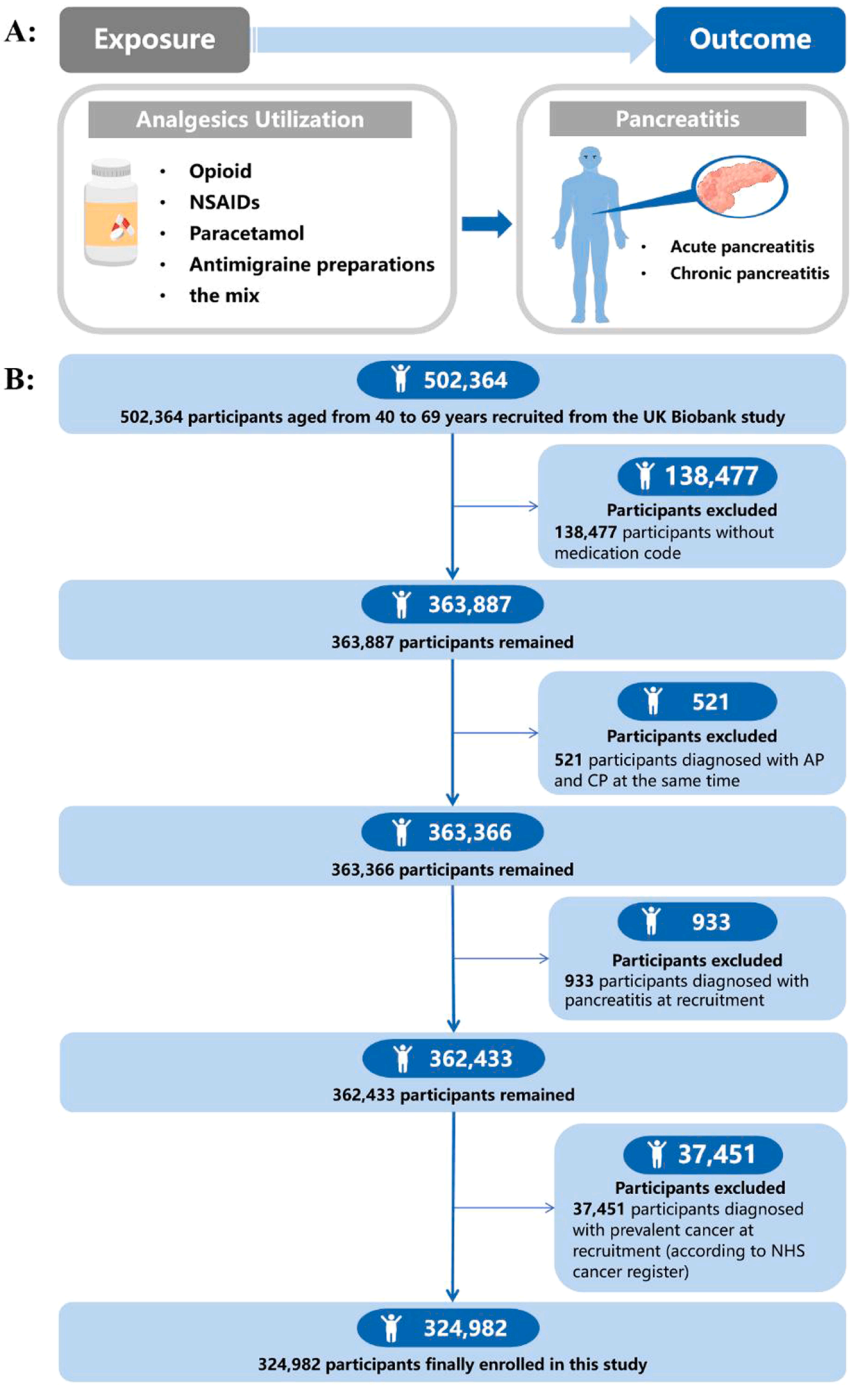

Fig. 1. Flowchart of the study participants.[a]

[a] The flowchart was drawn with *Figdraw* (https://www.figdraw.com/).

3.2. Analgesics utilization increases the risk of pancreatitis

Over a median follow-up period of 13.70 years (up to November 18, 2022), 2303 pancreatitis cases were documented. Within the analgesic cohort, 1430 cases of pancreatitis were identified, comprising 1198 cases of AP and 232 cases of CP. A positive association was observed between analgesics utilization and the risk of pancreatitis across all models, even though the strength of this association diminished with increased adjustment, from the minimally adjusted model (Model 1: HR 1.28, 95 % CI 1.18–1.40, $p < 0.001$) to the fully adjusted model (Model 3: HR 1.13, 95 % CI 1.04–1.23, $p = 0.004$). Similar trends were noted for both AP and CP (Table 2).

Further analysis was conducted to evaluate the association between types of analgesics utilization and the risk of pancreatitis, as illustrated in Fig. 2. The opioid group exhibited a higher risk of pancreatitis (HR 1.85, 95 % CI 1.49–2.31), as did the mixed group (HR 1.35, 95 % CI 1.21–1.51). Additionally, participants using opioids had a 73 % increased risk of AP (HR 1.73, 95 % CI 1.35–2.21) and a 166 % increased

Table 1
Population characteristics at baseline categorized by analgesics utilization ($n = 324,982$).

Characteristics	Overall ($n = 324,982$)	Non-analgesics group ($n = 144,322$)	Analgesics group ($n = 180,660$)	p [a]
Age, years, mean (SD)	57.14 (7.99)	57.13 (7.83)	57.16 (8.11)	0.379
Female, n (%)	181,747 (55.90)	81,169 (56.20)	100,578 (55.70)	0.001
White, n (%)	307,176 (94.50)	136,870 (94.80)	170,306 (94.30)	< 0.001
With college degree, n (%)	34,229 (10.50)	16,727 (11.60)	17,502 (9.70)	< 0.001
TDI [b]	−1.23 (3.13)	−1.47 (2.99)	−1.04 (3.22)	< 0.001
BMI, kg/m^2, mean (SD)	27.84 (4.96)	27.22 (4.65)	28.33 (5.14)	< 0.001
Current drinker, n (%)	296,405 (91.20)	133,611 (92.60)	162,794 (90.10)	< 0.001
Never smoker, n (%)	174,168 (53.60)	82,298 (57.00)	91,870 (50.90)	< 0.001
Physical activity [c], n (%)				< 0.001
Low	51,075 (15.70)	21,004 (14.60)	30,071 (16.60)	
Moderate	105,655 (32.50)	48,030 (33.30)	57,625 (31.90)	
High	101,100 (31.10)	47,202 (32.70)	53,898 (29.80)	
Missing	67,152 (20.70)	28,086 (19.50)	39,066 (21.60)	
Diabetes, n (%)	22,855 (7.10)	6743 (4.70)	16,112 (9.00)	< 0.001
Cholelithiasis, n (%)	6190 (1.90)	2322 (1.60)	3868 (2.10)	< 0.001
Number of pain sites, n (%)				< 0.001
0	112,426 (34.60)	67,318 (46.60)	45,108 (25.00)	
1	88,920 (27.40)	39,793 (27.60)	49,127 (27.20)	
2	59,289 (18.20)	21,248 (14.70)	38,041 (21.10)	
3	33,507 (10.30)	9539 (6.60)	23,968 (13.30)	
4	15,507 (4.80)	3612 (2.50)	11,895 (6.60)	
5	6089 (1.90)	1090 (0.80)	4999 (2.80)	
6	1825 (0.60)	296 (0.20)	1529 (0.80)	
7 or all over	7419 (2.30)	1426 (1.00)	5993 (3.30)	
Chronic pain, n (%)	159,772 (49.20)	51,560 (35.70)	108,212 (59.90)	< 0.001

Abbreviations: SD, standard deviation; TDI, Townsend deprivation index; BMI, body mass index; IPAQ, International Physical Activity Questionnaire; NSAIDs, non-steroidal anti-inflammatory drugs.

[a] P values were calculated by Chi-square tests (categorical variables) or F-tests (continuous variables).

[b] Participants were divided into tertiles based on the TDI.

[c] Physical activity was measured by IPAQ.

Table 2
The association between analgesics utilization and risk of pancreatitis.

	Person-years	Events (n)	Model 1		Model 2		Model 3		
			HR (95 % CI)	p	HR (95 % CI)	p	HR (95 % CI)	p	E value
Pancreatitis	2395,760	1430	1.28 (1.18, 1.40)	<0.001	1.17 (1.07, 1.27)	<0.001	1.13 (1.04, 1.23)	0.004	1.51 (1.24)
AP	2393,920	1198	1.26 (1.15, 1.38)	<0.001	1.14 (1.04, 1.25)	0.006	1.11 (1.01, 1.22)	0.024	1.46 (1.11)
CP	2386,703	232	1.41 (1.13, 1.75)	0.002	1.34 (1.07, 1.67)	0.009	1.25 (1.00, 1.56)	0.049	1.81 (1.00)

Abbreviations: HR, hazard ratio; CI, confidence interval; AP, acute pancreatitis; CP, chronic pancreatitis.
Model 1 was adjusted for age, sex, ethnicity, education, and Townsend deprivation index.
Model 2 was adjusted for age, sex, ethnicity, education, Townsend deprivation index, alcohol consumption status, smoking status, and physical activity.
Model 3 was adjusted for age, sex, ethnicity, education, Townsend deprivation index, alcohol consumption status, smoking status, physical activity, cholelithiasis, and diabetes.

risk of CP (HR 2.66, 95 % CI 1.59–4.44). Those using mixed analgesics had a 28 % increased risk of AP (HR 1.28, 95 % CI 1.14–1.45) and an 82 % increased risk of CP (HR 1.82, 95 % CI 1.38–2.39).

3.3. Subgroup analysis of association between analgesics utilization and pancreatitis

Subgroup analyses revealed that the association between analgesic use and pancreatitis risk (including AP) was significantly modified by cholelithiasis (p-interaction = 0.003 and 0.004, respectively). Regarding the risk of CP, a significant interaction between analgesics utilization and age was identified (p-interaction = 0.007) (Table 3). Other associations were not statistically significant. An increased risk of pancreatitis and AP was observed among participants without cholelithiasis. Additionally, older adults (> 60 years) in the analgesics group showed a positive correlation with the risk of CP (Table 4).

Furthermore, we investigated the impact of covariates on the association between types of analgesics utilization (the opioids group, the NSAIDs group, the paracetamol group, the antimigraine preparations group, and the mixed group) and the incidence of pancreatitis events (Table S4). Significant interactions were observed between types of analgesics utilization and both cholelithiasis and the number of pain sites concerning the risk of pancreatitis and AP (p-interaction < 0.05). Moreover, the impact of different types of analgesics utilization on the risk of CP was affected by age (p-interaction = 0.012).

Notably, an increased risk of pancreatitis was observed in participants without cholelithiasis who used opioids, paracetamol, or mixed analgesics, as well as in those with multiple pain sites upon using opioids or mixed analgesics (Table S5). Similar findings were observed in AP, except for participants without cholelithiasis using paracetamol (Table S6). Additionally, an elevated risk of CP was evident in older adults using opioids, paracetamol, and mixed analgesics. Conversely, an inverse correlation was observed between NSAIDs utilization and the risk of CP in younger adults (≤ 60 years) (Table S7).

4. Discussion

In this extensive prospective cohort study involving 324,982 individuals, we investigated the longitudinal association between analgesics utilization and the incidence of pancreatitis. Our findings indicated that the use of analgesics, particularly opioids and mixed analgesics, was associated with an increased risk of pancreatitis.

Pancreatitis is an auto-digestive disease of the pancreas with multiple etiologies. Beyond traditional etiological factors, such as alcohol and

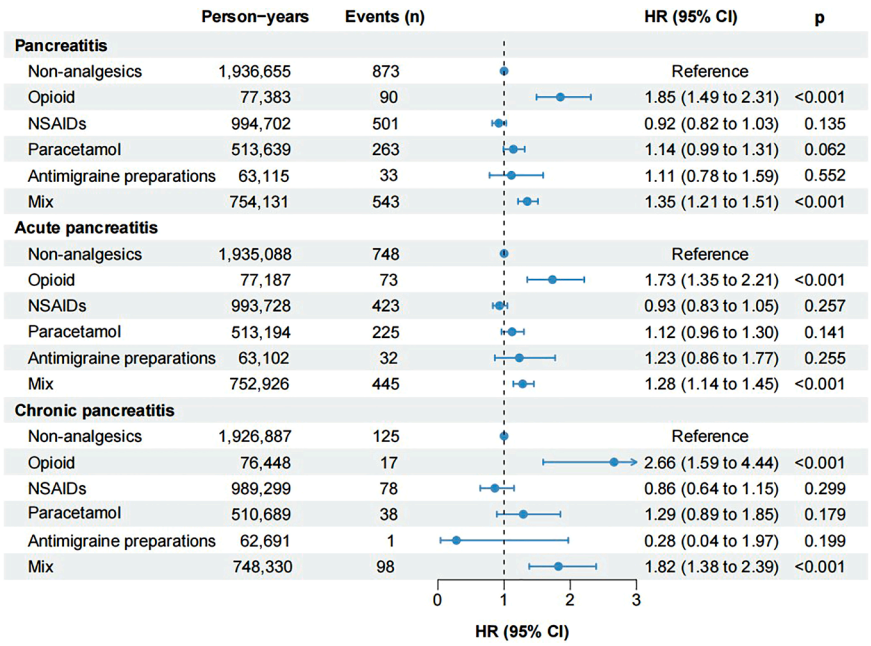

Fig. 2. Association between types of analgesics utilization and risk of pancreatitis
Notes: Model was adjusted for age, sex, ethnicity, education, Townsend deprivation index, alcohol consumption status, smoking status, physical activity, cholelithiasis, and diabetes.
Abbreviations: HR, hazard ratio; CI, confidence interval.

Table 3
P-interaction values between various subgroups and analgesics utilization.

	P values for interaction		
	Pancreatitis	Acute pancreatitis	Chronic pancreatitis
Age	0.160	0.692	**0.007**
Gender	0.721	0.895	0.080
Ethnicity	0.635	0.420	0.504
Education	0.896	0.725	0.667
TDI	0.945	0.856	0.706
BMI	0.155	0.076	0.178
Alcohol consumption	0.400	0.825	0.129
Smoking status	0.285	0.599	0.180
Physical activity	0.935	0.984	0.601
Diabetes	0.149	0.149	0.647
Cholelithiasis	**0.003**	**0.004**	0.531
Chronic pain	0.602	0.826	0.475
Number of pain site	0.456	0.721	0.169

Abbreviations: TDI, Townsend deprivation index; BMI, body mass index.

tobacco use, certain medications have also been implicated. Notably, although analgesics are conventionally used to manage pain in pancreatitis, emerging evidence suggests their potential role in disease initiation [7,8,11,12]. However, the current evidence linking medications to pancreatitis is primarily observational and of low quality. A systematic review utilized evidence-based classification criteria for drug-induced acute pancreatitis, and analgesics were notably absent from the high-confidence categories [22].

As a large population-based prospective cohort study, our study expands upon existing evidence, representing the first to thoroughly examine the association between analgesics (as well as different types of analgesics) and pancreatitis. Additionally, the findings of this study aid in differentiating between AP and CP. The analysis accounted for covariates to minimize the influence of confounding factors. Subgroup analyses were also performed to assess the interactive effects between exposure factors and covariates.

In the analysis utilizing Cox proportional hazards models, we found that analgesics utilization increased the risk of pancreatitis. This association persisted even after adjusting for potential confounding variables. Previous reviews have synthesized existing literature on the etiology of pancreatitis [6–8,13], compiling case reports of drug-induced pancreatitis linked to various pharmacological agents, including antineoplastic drugs, antibiotics, analgesics, etc. However, it is important to note that the list of analgesics in these reviews is not exhaustive, with paracetamol and combinations of medications being the primary examples provided [12,23]. In contrast to these studies, our study offers a more comprehensive analysis of the association between analgesics utilization and the risk of pancreatitis, and provides a thorough examination of the types of analgesics utilization.

In analyzing the association between specific analgesics and the risk of pancreatitis, a stronger correlation was observed in individuals using opioids compared to those not using analgesics. These findings align with previous studies, as four cases have reported that AP was associated with codeine intake, with cases indicating the recurrence of pancreatitis due to opioid use [24]. Additionally, two prospective cohort studies have identified an association between prolonged opioid exposure and the severity of AP in diagnosed patients, but a causal relationship has not yet been established [11,25]. Notably, our study focused on the onset of pancreatitis, investigating the relationship between opioid use and the risk of developing pancreatitis. While opioids may benefit AP patients by alleviating pain-induced stress responses, their use in unaffected populations could potentially increase the risk of pancreatitis. Mechanistically, opioid agonist receptors induce the contraction of sphincter of Oddi, leading to elevated pressure within the bile and pancreatic ducts, which may result in bile reflux. This refluxed bile can activate pancreatic enzymes, potentially causing inflammation and necrosis of pancreatic tissue [26–29]. We propose that this mechanism may contribute to the development of pancreatitis associated with opioid use. Additionally, opioids can also affect gastrointestinal motility, potentially impacting the overall function of the digestive system [30]. Our findings also indicated that the use of mixed analgesics was associated with an increased risk of pancreatitis. Two case reports indicate that a combination of acetaminophen and codeine may induce AP, complicating the identification of the specific causative medication [23].

Table 4
Association between analgesics utilization and pancreatitis according to different subgroups.

	HR (95 % CI)		
	Pancreatitis	Acute pancreatitis	Chronic pancreatitis
Age (years)			
≤ 60	1.05 (0.92, 1.19)	1.07 (0.94, 1.23)	0.91 (0.66, 1.26)
> 60	**1.22 (1.08, 1.38)**	**1.16 (1.02, 1.32)**	**1.65 (1.20, 2.26)**
Gender			
Female	**1.16 (1.02, 1.31)**	1.12 (0.98, 1.27)	**1.60 (1.08, 2.39)**
Male	1.11 (0.99, 1.26)	1.11 (0.97, 1.28)	1.11 (0.85, 1.45)
Ethnicity			
White	**1.13 (1.04, 1.23)**	**1.11 (1.01, 1.22)**	**1.27 (1.01, 1.60)**
Non-white	1.19 (0.78, 1.80)	1.26 (0.78, 2.02)	0.95 (0.38, 2.32)
Education			
College	1.08 (0.82, 1.42)	1.04 (0.77, 1.40)	1.25 (0.62, 2.52)
Non-college	**1.14 (1.04, 1.25)**	**1.12 (1.02, 1.24)**	1.24 (0.98, 1.57)
TDI [a]			
T1	1.14 (0.98, 1.34)	1.16 (0.98, 1.37)	1.05 (0.68, 1.61)
T2	1.10 (0.95, 1.28)	1.05 (0.90, 1.23)	1.48 (0.98, 2.23)
T3	**1.17 (1.01, 1.35)**	1.15 (0.98, 1.35)	1.25 (0.89, 1.75)
BMI (kg/m^2)			
≤ 25	1.13 (0.94, 1.36)	1.18 (0.96, 1.46)	1.00 (0.68, 1.45)
>25	**1.14 (1.03, 1.25)**	1.10 (0.99, 1.22)	**1.41 (1.07, 1.87)**
Alcohol consumption			
Never	1.09 (0.85, 1.40)	1.14 (0.86, 1.51)	0.90 (0.52, 1.57)
Current	**1.14 (1.04, 1.25)**	**1.11 (1.01, 1.23)**	**1.32 (1.04, 1.69)**
Smoking status			
Never	1.06 (0.93, 1.20)	1.07 (0.94, 1.22)	0.97 (0.68, 1.38)
Ever	**1.20 (1.07, 1.35)**	**1.16 (1.01, 1.32)**	**1.45 (1.09, 1.93)**
Physical activity [b]			
Low	1.17 (0.96, 1.43)	1.12 (0.90, 1.38)	1.55 (0.92, 2.61)
Moderate	1.14 (0.98, 1.33)	1.12 (0.94, 1.32)	1.28 (0.88, 1.87)
High	1.14 (0.96, 1.34)	1.13 (0.94, 1.35)	1.20 (0.78, 1.85)
Cholelithiasis			
No	**1.17 (1.07, 1.28)**	**1.15 (1.04, 1.27)**	**1.26 (1.00, 1.59)**
∃Yes	0.92 (0.72, 1.18)	0.91 (0.70, 1.17)	1.13 (0.50, 2.57)
Diabetes			
∃No	**1.14 (1.04, 1.25)**	**1.13 (1.02, 1.24)**	1.24 (0.97, 1.59)
∃Yes	1.03 (0.79, 1.34)	0.96 (0.71, 1.30)	1.28 (0.77, 2.14)
Chronic pain			
∃No	1.03 (0.91, 1.18)	1.04 (0.90, 1.19)	1.03 (0.73, 1.45)
∃Yes	1.12 (0.99, 1.26)	1.10 (0.96, 1.25)	1.23 (0.90, 1.67)
Number of pain site			
No	0.96 (0.82, 1.13)	0.97 (0.81, 1.16)	0.94 (0.62, 1.42)
∃≥1	**1.14 (1.02, 1.26)**	1.11 (0.99, 1.25)	1.28 (0.97, 1.69)

Abbreviations: HR, hazard ratio; CI, confidence interval; TDI, Townsend deprivation index; BMI, body mass index.
[a] Participants were divided into tertiles based on the TDI.
[b] Physical activity was measured by IPAQ.

In subgroup analysis, we found that age, cholelithiasis, and the number of pain sites influenced the association between analgesics and pancreatitis events. Compared to younger adults (≤ 60 years), older adults (> 60 years) had a higher risk of developing CP when using opioids, paracetamol, or mixed analgesics. The deterioration of organ function and the senescence of tissue cells increase the susceptibility of older adults to pancreatitis. Numerous studies suggest that age is a significant contributing factor to pancreatitis, with severe cases occurring more frequently in the elderly [31–34]. These findings align with our results. Additionally, our observations indicated that individuals without cholelithiasis exhibited an elevated risk of developing pancreatitis and AP when using opioids or mixed analgesics. In contrast, this significant association was not observed in individuals with cholelithiasis. Gallstones are among the most prevalent risk factors for pancreatitis [35], as they can obstruct the pancreatic duct, leading to increased pressure and the release of enzyme-rich fluid into the pancreas [36]. The absence of a significant association in individuals with cholelithiasis may be attributed to the fact that, compared to gallstones, which are well-established high-risk factors for pancreatitis, the relationship between analgesics and pancreatitis is less pronounced. Moreover, our findings suggested that individuals experiencing pain in multiple sites were at an elevated risk of developing pancreatitis as well as AP. A possible explanation for this is that pain may be associated with the release of inflammatory factors, potentially leading to inflammation of pancreatic tissue. Alternatively, the presence of more than five stratification factors in this subgroup analysis may increase the influence of random factors, thereby affecting the confidence in the results.

This study is subject to several limitations. Firstly, despite adjustments for some confounders, residual confounders cannot be excluded. For instance, patients with multimorbidity who require analgesics may possess an inherently elevated risk of pancreatitis due to systemic inflammation [37,38], and opioid users frequently present with comorbid alcohol misuse, a recognized risk factor for pancreatitis [39,40]. To account for these potential confounding variables, we performed subgroup analyses based on covariates such as alcohol consumption status, chronic pain, diabetes, and cholelithiasis. Additionally, in our sensitivity analysis, the E-value methodology suggested that the HR (1.13, 95 % CI 1.04–1.23) for incident pancreatitis could only be attributed to an unmeasured confounder associated with both analgesic use and the risk of pancreatitis by a risk ratio exceeding 1.51, surpassing the influence of the confounders measured in this study (Table 2). The corresponding E-value indicated that an unmeasured confounder could not be sufficient to the negate the effects of analgesic use on pancreatitis risk in this study. Secondly, the participants in the UK Biobank are volunteers aged 40–69 years, which may introduce selection bias and limit the generalizability of the findings. Further research is needed

across different age cohorts to enhance the robustness of these conclusions. Thirdly, due to the lack of granular detail of dosage and frequency of analgesics utilization in the UK Biobank, further investigations need to be conducted to figure out the impacts of the dosage and frequency of analgesics utilization on the risk of pancreatitis. Although the HRs observed in this study remained modest, the extensive utilization of analgesics underscores their significant public health implications [41, 42]. Consequently, clinicians should consider enhanced monitoring for pancreatitis in patients using opioids and mixed analgesics.

5. Conclusions

In conclusion, the findings of this large population-based prospective cohort study demonstrated a positive correlation between analgesics utilization and the risk of pancreatitis. A more pronounced association was observed among individuals who used opioids. Given the considerable morbidity associated with pancreatitis, these findings suggest a promising strategy for mitigating the incidence of this condition. Further experimental research is required to validate or challenge the observed association between analgesics utilization and pancreatitis risk and to explore the underlying mechanisms involved.

Funding sources

This work was supported by the Natural Science Foundation of China (grant numbers 82472736), the Science and Technology Innovation Program of Hunan Province (grant numbers 2022RC1020), the Wisdom Accumulation and Talent Cultivation Project of the Third Xiangya Hospital of Central South University (grant numbers YX202208), and the 2024 National Undergraduate Innovation and Entrepreneurship Training Program (project numbers S202410533106).

Ethics approval

The study was conducted according to the guidelines of the Declaration of Helsinki, and the UK Biobank obtained ethical approval from the National Health Service (NHS) North West Multi-Center Research Ethics Committee (protocol code 11/NW/0382).

Data availability

The data that support the findings of this study were obtained from the UK Biobank Resource under application number 103,631. The UK Biobank is an open access resource and bona fide researchers can apply to use the UK Biobank data (https://www.ukbiobank.ac.uk/).

CRediT authorship contribution statement

Jiayi Wang: Writing – review & editing, Methodology, Formal analysis, Data curation, Conceptualization. **Wanxin Long:** Writing – original draft, Formal analysis. **Zehong Qi:** Validation, Data curation. **Yangjie Liao:** Validation. **Jingbo Li:** Writing – review & editing, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no conflicts of interest.

Acknowledgments

We would like to express our gratitude to the participants for generously dedicating their time to take part in the UK Biobank study. This research has been conducted using UK Biobank Resource under Application Number 103631. This work uses data provided by patients and collected by the NHS as part of their care and support. The linked health data acknowledgement can be found at https://www.ukbiobank.ac.uk/enable-your-research/manage-your-project.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.clinre.2025.102616.

References

[1] Xiao AY, Tan MLY, Wu LM, Asrani VM, Windsor JA, Yadav D, et al. Global incidence and mortality of pancreatic diseases: a systematic review, meta-analysis, and meta-regression of population-based cohort studies. Lancet Gastroenterol Hepatol 2016;1(1):45–55.
[2] Peery AF, Crockett SD, Murphy CC, Jensen ET, Kim HP, Egberg MD, et al. Burden and cost of gastrointestinal, liver, and pancreatic diseases in the United States: update 2021. Gastroenterology 2022;162(2):621–44.
[3] Beyer G, Habtezion A, Werner J, Lerch MM, Mayerle J. Chronic pancreatitis. Lancet 2020;396(10249):499–512.
[4] Petrov MS, Yadav D. Global epidemiology and holistic prevention of pancreatitis. Nat Rev Gastroenterol Hepatol 2018;16(3):175–84.
[5] Mederos MA, Reber HA, Girgis MD. Acute Pancreatitis: A Review. Jama 2021;325 (4):382–90.
[6] Li D, Wang H, Qin C, Du D, Wang Y, Du Q, et al. Drug-induced acute pancreatitis: a real-world pharmacovigilance study using the FDA adverse event Reporting System database. Clin Pharmacol Ther 2024;115(3):535–44.
[7] Nitsche C, Maertin S, Scheiber J, Ritter CA, Lerch MM, Mayerle J. Drug-induced pancreatitis. Curr Gastroenterol Rep 2012;14(2):131–8.
[8] Simons-Linares CR, Elkhouly MA, Salazar MJ. Drug-induced acute pancreatitis in adults. Pancreas 2019;48(10):1263–73.
[9] Lancashire RJ, Cheng K, Langman MJ. Discrepancies between population-based data and adverse reaction reports in assessing drugs as causes of acute pancreatitis. Aliment Pharmacol Ther 2003;17(7):887–93.
[10] Santos R, Ursu O, Gaulton A, Bento AP, Donadi RS, Bologa CG, et al. A comprehensive map of molecular drug targets. Nat Rev Drug Discov 2016;16(1): 19–34.
[11] Pandanaboyana S, Knoph CS, Olesen SS, Jones M, Lucocq J, Samanta J, et al. Opioid analgesia and severity of acute pancreatitis: an international multicentre cohort study on pain management in acute pancreatitis. United Eur Gastroenterol J 2024;12(3):326–38.
[12] He YH, Lu L, Wang YF, Huang JS, Zhu WQ, Guo Y, et al. Acetaminophen-induced acute pancreatitis: a case report and literature review. World J Clin Cases 2018;6 (9):291–5.
[13] Badalov N, Baradarian R, Iswara K, Li J, Steinberg W, Tenner S. Drug-induced acute pancreatitis: an evidence-based review. Clin Gastroenterol Hepatol 2007;5 (6):648–61. e3.
[14] Sudlow C, Gallacher J, Allen N, Beral V, Burton P, Danesh J, et al. UK Biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. PLoS Med 2015;12(3):e1001779.
[15] Spagnolo DM, Greer PJ, Ohlsen CS, Mance S, Ellison M, Breze C, et al. Acute and chronic Pancreatitis Disease prevalence, classification, and comorbidities: a cohort study of the UK BioBank. Clin Transl Gastroenterol 2022;13(1):e00455.
[16] Ahmed Ali U, Issa Y, Hagenaars JC, Bakker OJ, van Goor H, Nieuwenhuijs VB, et al. Risk of recurrent pancreatitis and progression to chronic pancreatitis after a first episode of acute pancreatitis. Clin Gastroenterol Hepatol 2016;14(5):738–46.
[17] Drewes AM, Bouwense SAW, Campbell CM, Ceyhan GO, Delhaye M, Demir IE, et al. Guidelines for the understanding and management of pain in chronic pancreatitis. Pancreatology 2017;17(5):720–31.
[18] Sankaran SJ, Xiao AY, Wu LM, Windsor JA, Forsmark CE, Petrov MS. Frequency of progression from acute to chronic pancreatitis and risk factors: a meta-analysis. Gastroenterology 2015;149(6):1490–500. e1.
[19] Townsend J P. Deprivation. J Soc Policy 1987;16:125–46.
[20] Macfarlane GJ, Beasley M, Jones GT, Stannard C. The epidemiology of regular opioid use and its association with mortality: prospective cohort study of 466 486 UK biobank participants. EClinicalMedicine 2020;21:100321.
[21] VanderWeele TJ, Ding P. Sensitivity analysis in observational research: introducing the E-value. Ann Intern Med 2017;167(4):268–74.
[22] Saini J, Marino D, Badalov N, Vugelman M, Tenner S. Drug-induced acute pancreatitis: an evidence-based classification (Revised). Clin Transl Gastroenterol 2023;14(8):e00621.
[23] Locher C, Lambare B, Fischer D, Labayle D. [Acute pancreatitis induced by codeine-acetaminophen association: report of two cases]. Gastroenterol Clin Biol 2003;27 (1):124–5.
[24] Hastier P, Buckley MJ, Peten EP, Demuth N, Dumas R, Demarquay JF, et al. A new source of drug-induced acute pancreatitis: codeine. Am J Gastroenterol 2000;95 (11):3295–8.
[25] Knoph CS, Joseph N, Lucocq J, Olesen SS, Huang W, Dhar J, et al. No definite associations between opioid doses and severity of acute pancreatitis - results from a multicentre international prospective study. Pancreatology 2025;25(1):12–9.
[26] Economou G, Ward-McQuaid JN. A cross-over comparison of the effect of morphine, pethidine, pentazocine, and phenazocine on biliary pressure. Gut 1971; 12(3):218–21.
[27] Helm JF, Venu RP, Geenen JE, Hogan WJ, Dodds WJ, Toouli J, et al. Effects of morphine on the human sphincter of Oddi. Gut 1988;29(10):1402–7.

[28] Madácsy L, Bertalan V, Szepes A, Lonovics J. Effect of nalbuphine on the motility of the sphincter of Oddi in patients with suspected sphincter of Oddi dysfunction. Gastrointest Endosc 2003;57(3):319–23.
[29] Thompson DR. Narcotic analgesic effects on the sphincter of Oddi: a review of the data and therapeutic implications in treating pancreatitis. Am J Gastroenterol 2001;96(4):1266–72.
[30] Wu LM, Pendharkar SA, Asrani VM, Windsor JA, Petrov MS. Effect of intravenous fluids and analgesia on dysmotility in patients with acute pancreatitis: a prospective cohort study. Pancreas, 2017;46(7):858–66.
[31] Carvalho JR, Fernandes SR, Santos P, Moura CM, Antunes T, Velosa J. Acute pancreatitis in the elderly: a cause for increased concern? Eur J Gastroenterol Hepatol 2018;30(3):337–41.
[32] Fu S, Stanek A, Mueller CM, Brown NA, Huan C, Bluth MH, et al. Acute pancreatitis in aging animals: loss of pancreatitis-associated protein protection? World J Gastroenterol 2012;18(26):3379–88.
[33] Yang DD, Zuo HD, Wu CQ, Chen TW, Xue HD, Jin ZY, et al. The characteristics of acute necrotizing pancreatitis in different age stages: an MRI study. Eur J Radiol 2020;122:108752.
[34] Zhu Y, Pan X, Zeng H, He W, Xia L, Liu P, et al. A study on the etiology, severity, and mortality of 3260 patients with acute pancreatitis according to the revised Atlanta Classification in Jiangxi, China over an 8-year period. Pancreas 2017;46 (4):504–9.
[35] Zilio MB, Eyff TF, Azeredo-Da-Silva ALF, Bersch VP, Osvaldt AB. A systematic review and meta-analysis of the aetiology of acute pancreatitis. HPB (Oxford) 2019;21(3):259–67.
[36] Harvey MH, Wedgwood KR, Austin JA, Reber HA. Pancreatic duct pressure, duct permeability and acute pancreatitis. Br J Surg 1989;76(8):859–62.
[37] Quan Y, Yang XJ. Metabolic syndrome and acute pancreatitis: current status and future prospects. World J Gastroenterol 2024;30(45):4859–63.
[38] Zhang Z, Yuan M, Shi K, Xu C, Lin J, Shi Z, et al. Association between multimorbidity trajectories, healthcare utilization, and health expenditures among middle-aged and older adults: china Health and Retirement Longitudinal Study. J Affect Disord 2023;330:24–32.
[39] Esser MB, Guy Jr GP, Zhang K, Brewer RD. Binge drinking and prescription opioid misuse in the U.S., 2012-2014. Am J Prev Med 2019;57(2):197–208.
[40] Vowles KE, Witkiewitz K, Pielech M, Edwards KA, McEntee ML, Bailey RW, et al. Alcohol and opioid use in chronic pain: a cross-sectional examination of differences in functioning based on misuse status. J Pain 2018;19(10):1181–8.
[41] Duarte N, Martins JP, García-Pedraza J, Santos M. Ten-year analgesic utilization patterns and economic implications in Portugal. Br J Clin Pharmacol 2025;91(3): 866–81.
[42] Ni J, Tang X, Chen L. Medication overdose data analysis: a review of medication error reports in the FDA adverse event reporting system (FAERS). BMC Pharmacol Toxicol 2023;24(1):41.