Association between age at diabetes onset or diabetes duration and subsequent risk of pancreatic cancer: Results from a longitudinal cohort and mendelian randomization study

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Summary

Background The aim of the study is to estimate the incidence of pancreatic cancer among individuals with new-onset type 2 Diabetes (T2DM) and evaluate the relationship of pancreatic cancer risk with age at diabetes onset and diabetes duration.

Methods This longitudinal cohort study included 428,362 new-onset T2DM patients in Shanghai and Mendelian randomization (MR) in the east-Asian population were used to investigate the association. Incidence rates of pancreatic cancer in all patients and by subgroups were calculated and compared to the general population.

Findings A total of 1056 incident pancreatic cancer cases were identified during eight consecutive years of follow-up. The overall pancreatic cancer annual incidence rate was 55·28/100,000 person years in T2DM patients, higher than that in the general population, with a standardized incidence ratio (SIR) of 1·54 (95% confidence interval [CI], 1·45−1·64). The incidence of pancreatic cancer increased with age and a significantly higher incidence was observed in the older groups with T2DM. However, the relative pancreatic cancer risk was inversely related to age of T2DM onset, and a higher SIR of 5·73 (95%CI, 4·49−7·22) was observed in the 20−54 years old group. The risk of pancreatic

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cancer was elevated at any diabetes duration. Fasting blood glucose ≥10·0 mmol/L was associated with increased risk of pancreatic cancer. MR analysis indicated a positive association between T2DM and pancreatic cancer risk.

Interpretation Efforts toward early and close follow-up programs, especially in individuals with young-onset T2DM, and the improvement of glucose control might represent effective strategies for improving the detection and results of treatment of pancreatic cancer.

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Keywords: Type 2 diabetes mellitus; Pancreatic cancer; Onset age; Diabetes duration; Mendelian randomization

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Research in context

Evidence before this study

We searched PubMed for articles published in English up to December 31, 2021, using the terms "diabetes", "new-onset diabetes", "pancreatic cancer". The association between T2DM and the development of pancreatic cancer has been recognized for more than one century and diabetes is potentially a modifiable risk factor for pancreatic cancer. However, these studies included relatively small sample sizes of diabetes. Furthermore, few studies have investigated age of diabetes onset and diabetes duration in relation to the incidence of pancreatic cancer across a large population. In 2020, The Lancet Oncology, The Lancet Gastroenterology & Hepatology, and EBioMedicine presented a cross-journal series of four reviews highlighting the progress being made in all areas of pancreatic cancer research and emphasized that in order to work together to reduce the burden of pancreatic cancer, effective strategies for improving the detection and results of treatment of pancreatic cancer needed to be explored in new clinical studies.

Added value of this study

The present study is the largest study in China to investigate the association of pancreatic cancer and new-onset T2DM. The key findings can be summarized as three points: (1) Patients with new-onset T2DM have a higher risk of pancreatic cancer in both males and females among Chinese adults when compared to those in the general population, where causality was suggested by MR analysis in an East-Asian population; (2) Our study investigated both the absolute and relative risk of pancreatic cancer across different age groups and found for the first time, to our knowledge, that although the absolute risk of pancreatic cancer increased with age, the relative risk of pancreatic cancer was inversely related to age at onset of T2DM; (3) This is the first report of pancreatic cancer and diabetes duration in a large-scale T2DM study. Patients with T2DM diagnosed more than 5 years and those with higher FBG levels had increased risk of pancreatic cancer.

Implications of all the available evidence

New-onset T2DM had a significantly association with a higher risk of pancreatic cancer among East-Asian adults. Young-onset T2DM had notably higher relative risk of pancreatic cancer. Patients with T2DM diagnosed more than 5 years and with elevated FBG levels had increased risk of pancreatic cancer. Efforts toward early and close follow-up programs, especially in individuals with young-onset T2DM, and the improvement of glucose control might represent effective strategies for improving the detection and results of treatment of pancreatic cancer.

Introduction

Pancreatic cancer is one of the leading causes of cancer mortality around the world and in China.[1] The prognosis of pancreatic cancer is typically worse than that of most other tumors, and the 5-year survival rate is less than 5%. In 2020, The Lancet Oncology, The Lancet Gastroenterology & Hepatology, and EBioMedicine presented a cross-journal series of four reviews highlighting the progress being made in all areas of pancreatic cancer research and emphasized the need to work together to reduce the burden of pancreatic cancer. Previous studies showed that early diagnosis and treatment can improve the overall prognosis of pancreatic cancer.[2,3] However, in the general population, screening of large groups is not considered feasible to detect the disease at its early stage. The key to diagnosis and treatment is to identify the population at high-risk of pancreatic cancer as early as possible.[4,5]

A number of modifiable risk factors have been identified for pancreatic cancer, including smoking, obesity, and alcohol use, while age and familial cancer syndromes are regarded as nonmodifiable risk factors for the disease. Diabetes is potentially a modifiable risk factor for pancreatic cancer in populations of the Asia-Pacific region.[6] The global prevalence of T2DM is

growing and the increase of T2DM in Asia is predicted to be higher and faster than other continents. Due to the rapid development of the economy and dramatic change of lifestyle, the prevalence of T2DM was reported to be 12·8% in China, revealing a rapid increase over the past 30 years.[7,8] Impaired glucose metabolism is associated with adverse macro- and micro- vascular outcomes, and with a higher incidence of cancers.[9,10] The association between T2DM and the development of pancreatic cancer has indeed been recognized for more than one century.[11] Convincing evidence has indicated that T2DM is associated with an increased risk for pancreatic cancer and that T2DM can worsen cancer stage and increase cancer-related mortality.[12,13]

However, few studies have investigated age of diabetes onset and diabetes duration in relation to the incidence of pancreatic cancer across a large population. Further, little is known about the effect of various levels of fasting blood glucose (FBG) on the risk of pancreatic cancer among patients with new-onset T2DM.[14] In the present analysis, we studied the association between age of diabetes onset and diabetes duration with pancreatic cancer, investigated the relationship of various levels of FBG to the risk of pancreatic cancer, and used two-sample Mendelian randomization (MR) to investigate additional evidence supporting a causal relationship between type 2 diabetes and pancreatic cancer in a separate east Asian population (Figure 1).

Methods

Study design and population

We performed a longitudinal cohort study to assess the association of type 2 diabetes with the risk of pancreatic cancer. Analysis was performed on data collected from the Shanghai Standardized Diabetes Management System (SSDMS), operated by the Shanghai Municipal Center for Disease Control and Prevention (SCDC). The system was initiated in 2004 and well-established, covering overall 241 community health service centers in 16 districts of Shanghai after the launch of the National Basic Public Health Service Program (NBPHSP) in 2009.[15] According to the requirement of the NBPHSP in Shanghai, community health centers (CHCs) are responsible for providing management for T2DM patients and for uploading electronic records to SSDMS. All diagnosed cases of T2DM in Shanghai were required to register in the system, including newly diagnosed cases through community-based screenings or physical examinations and recently diagnosed cases through routine outpatient visits.[16] In order to ensure the accuracy and reliability of registration management information, the SCDC organized for the 16 district CDC to randomly select a proportion of patients with type 2 diabetes for quality control in the form of annual telephone and face-to-face investigation. T1DM patients were not included in the system. Baseline information for each
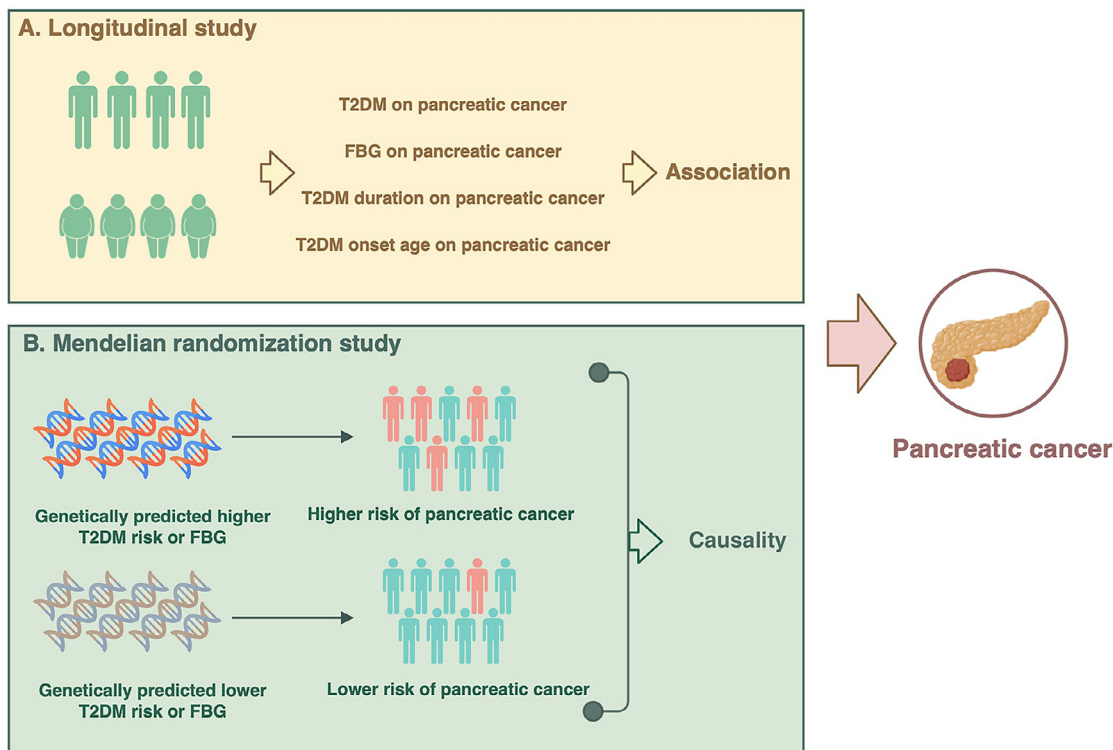

Figure 1. Association and causal effect of T2DM and pancreatic cancer.

case of T2DM in the SSDMS, including height, weight, blood pressure and blood glucose were collected during an initial assessment at registration. Medication use, smoking history, alcohol consumption, and physical activity were not available from all patients in the current system and were not included in the present analysis.

A malignant tumor registration and reporting system was established in Shanghai in 1963. In 2002, according to the requirement of the Shanghai malignant tumor reporting measures, the SCDC was fully responsible for the malignant tumor registry, which established a population-based tumor registration and reporting information system. The malignant tumor registry covered all new cases of malignant tumors, tumor deaths and survival data in Shanghai's residents. In accordance with the requirements of the measures of Shanghai Municipality on the reporting of malignant tumors, all medical institutions in Shanghai report new cases of malignant tumors which were found during outpatient, emergency and inpatient treatment. The medical staff responsible for cancer diagnosis and treatment completes the "Shanghai tumor case report card" following diagnosis to register the information into the malignant tumor registry. The relevant technical standards issued by the International Agency for Research on Cancer (IARC) and the relevant technical requirements issued by the National Office of Cancer Prevention and Treatment were used for tumor registration.[17] In order to ensure the integrity of the reported information, the SCDC regularly organized for the 16 district centers to carry out missing report investigations at relevant medical institutions every year. The prevalence of missing reports was found to be 0.5%. The classification of tumor location was coded according to the ICD-10 codes. Pancreatic cancers were defined based on ICD-10 codes C25.

From January 2011 to the end of 2018, a total of 428,568 new-onset T2DM patients had been registered in the SSDMS. The median time from the diagnosis of T2DM to registration was 8.6 months. New cases of pancreatic cancer were identified through the malignant tumor registry system during an 8-year period. The geographic distribution of both registries are for exactly the same regions including all 16 districts of Shanghai. From January 2011, the ID card number was matched between the diabetes management system and the malignant tumor registry system, allowing investigation of the relationship between tumors and diabetes mellitus.

In order to eliminate T2DM caused by islet destruction by pancreatic cancer, we excluded 206 T2DM patients in whom the pancreatic cancer was diagnosed before or at the same time of the confirmation of T2DM (Supplemental Figure 1 and Supplemental Table 1). Patients were censored if they were lost to follow-up, died of other causes, moved out of Shanghai or reached the end of the study.

This study was approved by the Ethical Review Committee of Shanghai Municipal Center for Disease Control and Prevention, and the requirement for informed consent was exempted.

Related definitions

Participants were identified as having T2DM if FBG level $\geq$ 7.0 mmol/L and/or a 2-hour glucose (after 75 g oral glucose tolerance test) level $\geq$ 11.1 mmol/L or use of antidiabetic medication according to the WHO criteria.[18] The first fasting glucose value when patients registered in the SSDMS was considered in ascertaining the relationship between glucose and pancreatic cancer risk. The following subgroups of FBG were used for certain analyses: <6.0 mmol/L, 6.0−7.9 mmol/L, 8.0−9.9 mmol/L and $\geq$ 10.0 mmol/L according to the Chinese Expert Consensus on Management of Diabetes in Chinese Adults.[19] The patients with T2DM were classified into four age groups: 20−54 years old, 55−64 years old, 65−74 years old and $\geq$ 75 years old. BMI was calculated as weight (kg) divided by the square of height (m).

Statistical analyses

Baseline characteristics were summarized by pancreatic cancer status and by sex, categorical data were presented as number and percentage, and continuous variables presented as mean and standard deviation. The age-standardized rates (ASRs; per 100,000 person years) were calculated using the direct method, based on the sixth nationwide population census by age groups and age-specific incidence. Person-years (PYs) of follow-up were calculated from the date when T2DM was first diagnosed to the date of diagnosis with pancreatic cancer, the date of loss to follow-up, or the cutoff date of the study, December 31, 2018. The standardized incidence ratio (SIR) was calculated as the ratio between the observed and the expected number of pancreatic cancers in each year. The expected number was defined by multiplying the accumulated PYs of follow-up in each year by cancer incidence rate in the Shanghai tumor registry system. The annual incidence in the general population was calculated by dividing the number of incident pancreatic cancers by the number of adults aged 20 years or older in the Shanghai general population from 2011 to 2015. When we prepared the data until Dec, 31 2018, the Shanghai Cancer Report only updated to 2015. So, we used the general denominator data from 2011 to 2015. The 95% confidence intervals (95% CI) for the SIR were based on the assumption that the number of observed cases followed a Poisson distribution. The overall or group-specific incidence rate of pancreatic cancer was calculated by dividing the number of incident pancreatic cancer cases by person-years of follow-up.

A log-rank test was used to examine the difference in pancreatic cancer incidence rates across age at diagnosis, diabetes duration, FBG and BMI subgroups and Kaplan-Meier survival curves were plotted by FBG

category. Cox proportional hazards regression models were applied to assess the relationship of FBG levels to the risk of pancreatic cancer. FBG levels were used as continuous variables and confounding variables including age, sex and SBP were adjusted for in the model. Analyses were undertaken in participants overall and by sex. Statistical analyses were performed using the SAS software (version 9.4; SAS Institute, Inc., Cary, North Carolina). *P* values < 0·05 were considered statistically significant.

Mendelian randomization

To identify potential causal links between FBG level, T2DM and pancreatic cancer, we performed two-sample MR analyses using the TwoSampleMR (v.0.5.5) and MRPRESSO (v1.0) package.[20,21] We used T2DM and FBG (in non-diabetic people) as exposures in our MR. The Asian Genetic Epidemiology Network performed a large genome-wide association study (GWAS) of T2DM in the east Asian population.[22] The Meta-Analyses of Glucose and Insulin-related traits Consortium provided Asia-ancestry GWAS summary statistics of FBG level in participants without T2DM.[23] The GWAS of pancreatic cancer was extracted from the biobank in east-Asian population, the Biobank of Japan (BBJ).[24]

For MR analyses, we selected independent single nucleotide polymorphism (SNP) associated with T2DM or FBG at the genome-wide significant level ($P < 5 \times 10^{-8}$) and linkage disequilibrium based on $r^2 < 0.1$. When no shared SNPs were available between exposures and outcome, proxies with $r^2 > 0.8$ were added. Finally, the remained SNPs were considered as valid instruments variants (IVs) used in MR.

MR causality tests were performed using the inverse-variance weighted method by meta-analyzing the effect of each IV from Wald ratio. We also estimated the causality using additional methods: Weighted median, MR-Egger, and MR-PRESSO. Heterogeneity of the results was assessed using Cochran's Q statistic and leave-one-out analyses. Pleiotropy was assessed using MR-Egger intercept and MR-PRESSO outliers-adjusted test.

Role of the funding source

The study funder had no role in the study design; collection, analysis, and interpretation of data; or report writing. The corresponding authors had full access to the data and have final responsibility for publication.

Results

Baseline characteristics

A total of 428,362 patients (mean age, 63·81±11·10 years) with new-onset T2DM were investigated in this study, including 205,694 males (48·02%) and 222,668 females (51·98%). Baseline characteristics are shown by

pancreatic cancer status in Table 1 and by sex in Supplemental Table 2. Compared to males with T2DM, females were older (64·61±10·87 vs. 62·94±11·27 years, *P*<0·0001) and had lower FBG (7·18±1·61 vs. 7·34±1·81, *P*<0·0001). Compared to patients without pancreatic cancer, patients with pancreatic cancer were older (69·71±9·93 *vs.* 63·80±11·09, *P*<0·0001), had lower BMI (23·80±3·24 vs. 24·43±3·11 kg/m², *P*<0·0001) and had higher FBG (7·69±2·46 vs. 7·26±1·71 mmol/L, *P*<0·0001) respectively. Patients with pancreatic cancer diagnosed within 12 months after the diagnosis of T2DM had lower BMI (23·13±3·08 kg/m²) and higher glucose (8·24±3·13 mmol/L) at baseline than the respective levels in those diagnosed more than 12 months after diagnosis of diabetes (Supplemental Table 3).

The incidence rate of pancreatic cancer

A total of 1,056 incident pancreatic cancer cases were identified during the study period in patients followed from the time of diagnosis of T2DM, with a mean follow-up of 4·5±2·2 years. The crude incidence rates of pancreatic cancer were 55·28 per 100.000 PYs (95%CI, 51·99−58·69) in all T2DM patients, and 59·61 (95%CI, 54·68−64·80) and 51·38 (95%CI, 47·05−55·96) per 100,000 PYs in males and females, respectively. Overall, the ASR of pancreatic cancer in patients with T2DM was 20·75/100,000 PYs (95%CI, 18·95−22·54). The SIRs of pancreatic cancer in T2DM vs general population were 1·54 (95%CI, 1·45−1·64) in all T2DM patients, 1·54 (95%CI, 1·41−1·67) in males and 1·57(95%CI, 1·44−1·71) in females (Table 2).

The absolute and relative risk of pancreatic cancer across different ages at onset

The annual incidence of pancreatic cancer increased from 17·62 per 100,000 PYs in those with age of diagnosis of T2DM 20−54 years to 40·76 in patients aged 55−64 years, 68·45 in those aged 65−74 years and 120·45 per 100,000 PYs in patients ≥75 years old. A significantly higher incidence of pancreatic cancer was observed in the older groups with T2DM. The relative pancreatic cancer risk was presented as the SIR, which was inversely related to age at onset of T2DM. A significantly higher SIR of 5·73 (95%CI, 4·49−7·22) was observed in those with age of diagnosis of T2DM 20−54 years, while SIRs were 1·91(95%CI, 1·70−2·14) in patients aged 55−64 years, 1·46 (95%CI, 1·30−1·62) in those aged 65−74 years and 1·24(95%CI, 1·12−1·37) in those new-onset T2DM group aged ≥75 years old. There were similar patterns in males and females analyzed separately (Table 2 and Figure 2). After excluding patients in whom the pancreatic cancer was diagnosed before or within six months after confirmation of T2DM, the incidence of pancreatic cancer in the cohort

	No pancreatic cancer	Pancreatic cancer	P value
Total, n	427306	1056	..
Age, years	63·80 (52·71−74·89)	69·71 (59·78−79·64)	<0·0001
Age, years (category)	..	..	<0·0001
20−54	83742 (19·60)	72 (6·82)	..
55−64	159443 (37·31)	296 (28·03)	..
65−74	112435 (26·31)	324 (30·68)	..
75−	71686 (16·78)	364 (34·47)	..
BMI, Kg/m^2	24·43 (21·32−27·54)	23·80 (20·56−27·04)	<0·0001
FPG, mmol/L	7·26 (5·55−8·97)	7·69 (5·23−10·15)	<0·0001
FPG, mmol/L (category)			<0·0001
<6·0	43410 (11·00)	103 (10·96)	..
6·0−7·9	269591 (68·34)	572 (60·85)	..
8·0−9·9	57870 (14·67)	158 (16·81)	..
≥10	23595 (5·98)	107 (11·38)	..
Male, n	205155	539	..
Age, years	62·93 (51·66−74·20)	68·58 (58·73−78·43)	<0·0001
Age, years (category)	..	..	<0·0001
20−54	45117 (21·99)	47 (8·72)	..
55−64	75886 (36·99)	159 (29·50)	..
65−74	53664 (26·16)	174 (32·28)	..
75−	30488 (14·86)	159 (29·50)	..
BMI, Kg/m^2	24·41 (21·50−27·32)	23·80 (20·92−26·68)	<0·0001
FPG, mmol/L	7·34 (5·53−9·15)	7·77 (5·17−10·37)	<0·0001
FPG, mmol/L (category)	..	..	<0·0001
<6·0	19944 (10·54)	58 (12·08)	..
6·0−7·9	127010 (67·09)	283 (58·96)	..
8·0−9·9	29254 (15·45)	78 (16·25)	..
≥10	13092 (6·92)	61 (12·71)	..
Female, n	222151	517	..
Age, years	64·60 (53·73−75·47)	70·88 (60·99−80·77)	<0·0001
Age, years (category)	..	..	<0·0001
20−54	38625 (17·39)	25 (4·84)	..
55−64	83557 (37·61)	137 (26·50)	..
65−74	58771 (26·46)	150 (29·01)	..
75−	41198 (18·55)	205 (39·65)	..
BMI, Kg/m^2	24·45 (21·17−27·73)	24·23 (20·66−27·80)	<0·0001
FPG, mmol/L	7·18 (5·58−8·78)	7·60 (5·29−9·91)	<0·0001
FPG, mmol/L (category)	..	..	<0·0001
<6·0	23466 (11·44)	45 (9·78)	..
6·0−7·9	142581 (69·50)	289 (62·83)	..
8·0−9·9	28616 (13·95)	80 (17·39)	..
≥10	10503 (5·12)	46 (10·00)	..

Table 1: **Baseline characteristics of individuals with and without pancreatic cancer in the cohort of new-onset T2DM.**

across sex and age groups presented similar patterns as shown in Supplemental Table 6.

The association of diabetes duration and the risk of pancreatic cancer

We investigated the association of pancreatic cancer and T2DM duration by every12 months. As shown in Figure 3 and Supplemental Table 4, new-onset T2DM was significantly associated with elevated risk of pancreatic cancer in all eight years follow-up, with the higher crude rate and SIR among T2DM diagnosed within ≤ 1 year (64·31; 1·73), within the 6-year (58·55;1·73), the 7-year (59·47; 1·79) and more than 7 years (57·42; 1·78). Similar patterns were seen in males and females analyzed separately.

	General population				DM population						
	Population at risk	Number of pancreatic cancer cases	Annual incidence per 100,000 person years		Population at risk	Number of pancreatic cancer cases	Annual incidence per 100,000 person years		Standardized incidence ratios	
			Estimate	95% CI			Estimate	95% CI	Estimate	95% CI
Total, year ages	62639100	13119	20·94	20·59—21·31	428362	1056	55·28	51·99—58·69	1·54	1·45—1·64
20—54	35565903	1093	3·07	2·89—3·26	83814	72	17·62	13·79—22·05	5·73	4·49—7·22
55—64	14405920	3078	21·37	20·62—22·13	159739	296	40·76	36·25—45·61	1·91	1·70—2·14
65—74	6692647	3145	46·99	45·36—48·66	112759	324	68·45	61·20—76·1	1·46	1·30—1·62
75—	5974630	5803	97·13	94·64—99·66	72050	364	120·45	108·39—133·31	1·24	1·12—1·37
Male, year ages	31034169	7070	22·78	22·25—23·32	205694	539	59·61	54·68—64·80	1·54	1·41—1·67
20—54	17970992	730	4·06	3·77—4·37	45164	47	21·75	15·98—28·66	5·36	3·93—7·12
55—64	7192641	1913	26·60	25·42—27·82	76045	159	46·77	39·78—54·47	1·76	1·50—2·05
65—74	3354683	1840	54·85	52·37—57·41	53838	174	78·14	66·96—90·41	1·42	1·22—1·65
75—	2515853	2587	102·83	98·90—106·87	30647	159	126·68	107·75—147·54	1·23	1·05—1·44
Female, year ages	31604931	6049	19·14	18·66—19·63	222668	517	51·38	47·05—55·6	1·57	1·44—1·71
20—54	17594911	363	2·06	1·86—2·29	38650	25	12·98	8·40—18·85	6·29	4·07—9·29
55—64	7213279	1165	16·15	15·24—17·11	83694	137	35·47	29·78—41·80	2·20	1·84—2·60
65—74	3337964	1305	39·10	37·00—41·28	58921	150	59·84	50·64—70·00	1·53	1·30—1·80
75—	3458777	3216	92·98	89·79—96·25	41403	205	116·03	100·69—132·74	1·25	1·08—1·43

Table 2: **Incidence of pancreatic cancer in general population of Shanghai and the cohort of new-onset T2DM across sex and age at onset of diabetes groups.**

Articles

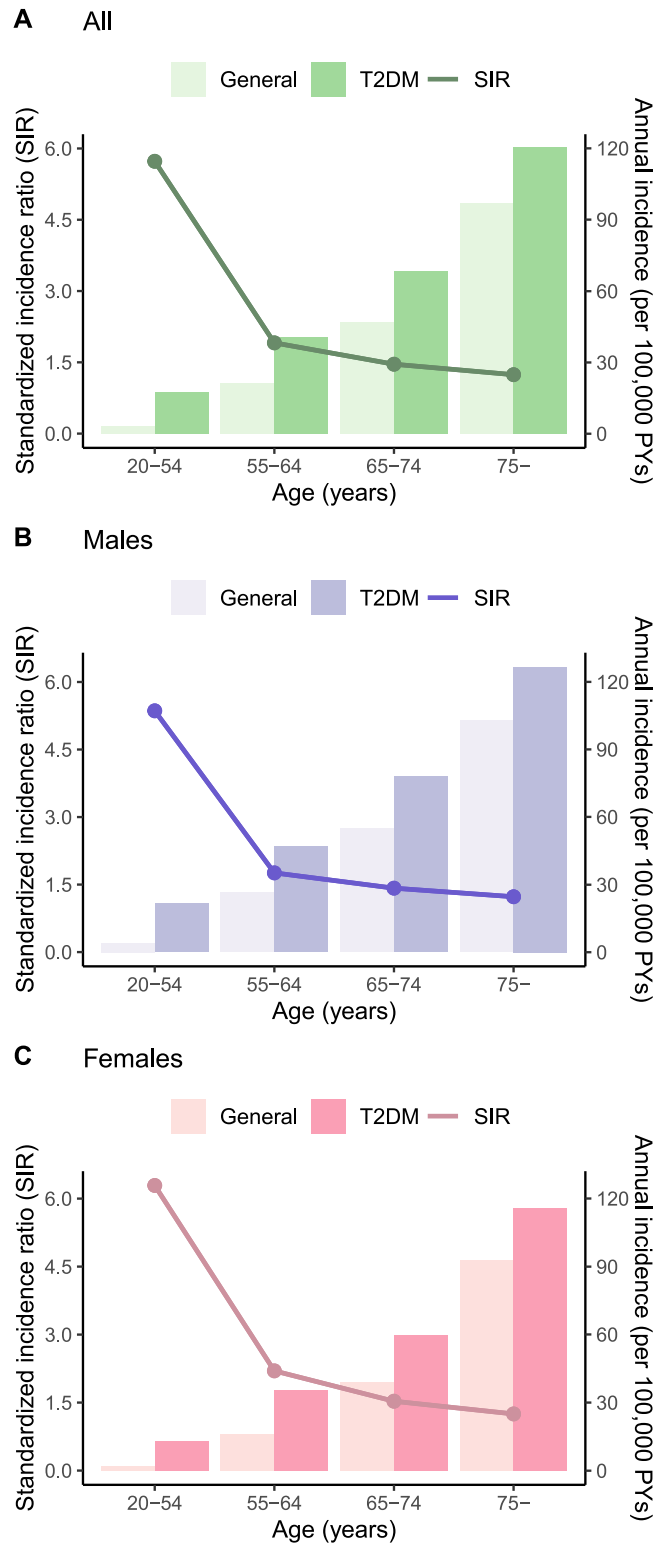**A   All**

B   Males

C   Females

Figure 2. The absolute and relative risk of pancreatic cancer with new-onset T2DM patients across different age groups (A: all T2DM patients; B: males; C: females).
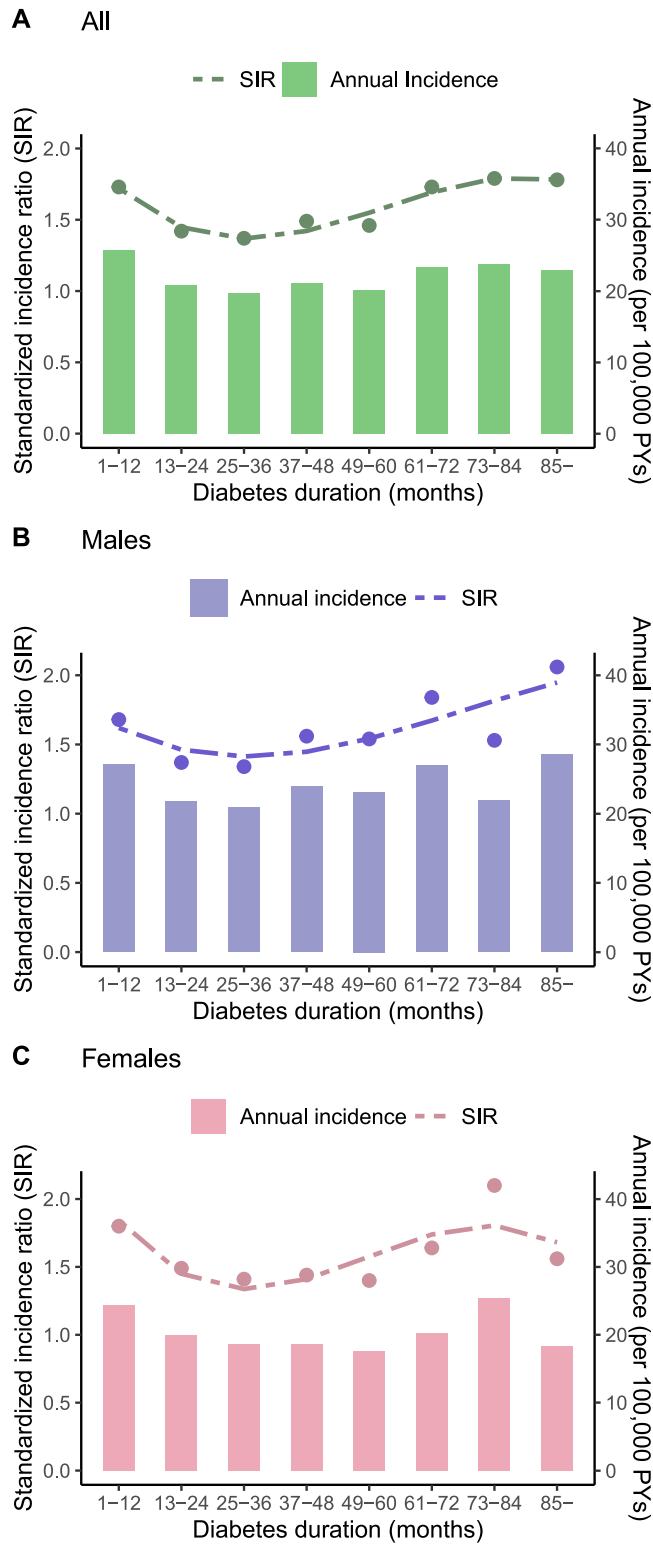
A All

B Males

C Females

Figure 3. The absolute and relative risk of pancreatic cancer with new-onset T2DM patients across different diabetes durations groups (A: all T2DM patients; B: males; C: females).

	No. of cases	No. at risk	Rate/100,000 person years	Adjusted HR (95% CI)*
Total				
<6·0	103	43513	52·70	1 (ref)
6·0−7·9	572	270163	47·40	0·90 (0·73−1·12)
8·0−9·9	158	58028	62·47	1·29 (0·99−1·66)
≥10	107	23702	107·01	2·35 (1·77−3·13)
Male				
<6·0	58	20002	65·30	1 (ref)
6·0−7·9	283	127293	50·43	0·82 (0·61−1·11)
8·0−9·9	78	29332	62·03	1·13 (0·79−1·62)
≥10	61	13153	112·36	2·25 (1·54−3·29)
Female				
<6·0	45	23511	42·21	1 (ref)
6·0−7·9	289	142870	44·76	0·99 (0·72−1·37)
8·0−9·9	80	28696	62·91	1·46 (1·00−2·13)
≥10	46	10549	100·67	2·41 (1·56−3·72)

Table 3: Pancreatic cancer in relation to FBG levels in patients with new-onset T2DM.
*Adjusted for age, sex, BMI and SBP in all subjects and adjusted for age, BMI and SBP in males and females.

The association of FBG levels and the risk of pancreatic cancer

We studied the relationship of various FBG levels to the risk of pancreatic cancer among patients with new-onset T2DM. In categorical analysis, the group with FBG ≥ 10·0 mmol/L has significantly higher pancreatic cancer risk than that of the groups with lower FBG. The hazard ratio for pancreatic cancer among patients with FBG ≥ 10·0 mmol/L was 2·35 (95% CI; 1·77−3·13) compared to those with FBG <6·0 mmol/L (Table 3 and Supplemental Figure 2). After adjustment for sex, age, BMI, and SBP, spline curves demonstrated a log linear relationship between FBG and the risk of pancreatic cancer in all subjects. The similar association pattern was seen in males and females after adjustment for age, BMI, and SBP (Table 3 and Supplemental Figure 3, $P<0.0001$). After excluding patients in whom pancreatic cancer was diagnosed before or within six months after confirmation of T2DM, the association of pancreatic cancer and FBG levels in patients with new-onset T2DM showed similar patterns (Supplemental Table 7).

The association of combined age at onset and FBG levels with the risk of pancreatic cancer

We assessed the effects on the risk of pancreatic cancer among patients stratified according to four age at onset categories and two FBG categories combined. The highest incidence of pancreatic cancer (250·25 per 100.000 PYs) was observed in those aged ≥75 years old having FBG ≥ 10·0 mmol/L. The highest SIR of 16·73 (95%CI; 9·37−27·59) was observed in those with age of diagnosis of T2DM 20−54 years having FBG ≥ 10·0 mmol/L (Supplemental Tables 5).
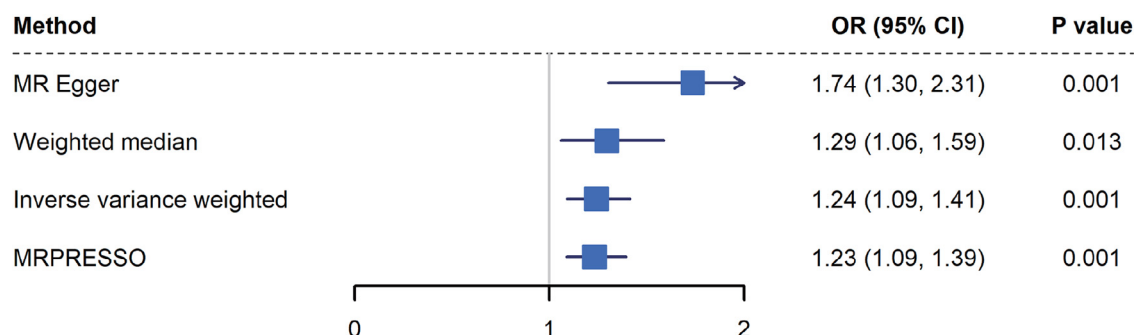
Causal relationship between T2DM and pancreatic cancer

T2DM is suggested to be associated with a 24% increase of pancreatic cancer risk (OR: 1.24, 95% CI: 1.09−1.41, p = 0.001) in the east Asian population. However, increased FBG level in the normal range is not causally associated with pancreatic cancer risk (p= 0.577). Sensitivity analyses from Weighted median, MR-Egger and MR-PRESSO methods are similar to the primary results (Figure 4).

Discussion

In the present study, we collected information on new-onset T2DM and pancreatic cancer over eight consecutive years. The key findings can be summarized as three points: (1) Patients with new-onset T2DM have a higher risk of pancreatic cancer in both males and females among Chinese adults when compared to those in the general population, where causality was suggested by MR analysis in an east-Asian population; (2) Our study investigated both the absolute and relative risk of pancreatic cancer across different age groups and found for the first time, to our knowledge, that although the absolute risk of pancreatic cancer increased with age, the relative risk of pancreatic cancer was inversely related to age at onset of T2DM, with a significantly higher SIR of 5·73 observed in those aged 20−54 years at onset of T2DM; (3) We firstly reported the risk of pancreatic cancer and overall diabetes duration in a large-scale T2DM study. Patients with diabetes diagnosed more than 5 years and those with higher FBG levels had increased risk of pancreatic cancer, with the risk of 2·35 times among those with FBG ≥ 10·0 mmol/L compared to those with FBG < 6·0 mmol/L.

The association between T2DM and the development of pancreatic cancer has been investigated for more than one century.[11,25,26] However, the observational results varied across different races and regions. In a US cohort from female participants in the Nurses' Health Study and male participants in the Health Professionals Follow-Up Study, recent-onset diabetes had 2·97-fold increased risk of pancreatic cancer and long-standing diabetes had 2·16 -fold increased risk of pancreatic cancer when compared with no diabetes.[27] A recent meta-analysis of 26 case-control studies in China involving 7,702 pancreatic cancer cases and 10,186 controls produced pooled results showing that patients with T2DM had an overall 3·69-fold (95% CI; 3·12−4·37) increased risk of pancreatic cancer compared to the risk in the general population.[28] The present study was consistent with the studies mentioned above and identified positive association between T2DM and

A. T2DM on pancreatic cancer

Method		OR (95% CI)	P value
MR Egger		1.74 (1.30, 2.31)	0.001
Weighted median		1.29 (1.06, 1.59)	0.013
Inverse variance weighted		1.24 (1.09, 1.41)	0.001
MRPRESSO		1.23 (1.09, 1.39)	0.001

B. FBG (non-diabetic) on pancreatic cancer

Method		OR (95% CI)	P value
MR Egger		2.07 (0.05, 80.24)	0.705
Weighted median		1.48 (0.30, 7.32)	0.634
Inverse variance weighted		1.43 (0.41, 5.02)	0.577
MRPRESSO		1.12 (0.40, 3.15)	0.836

OR (95% CI)
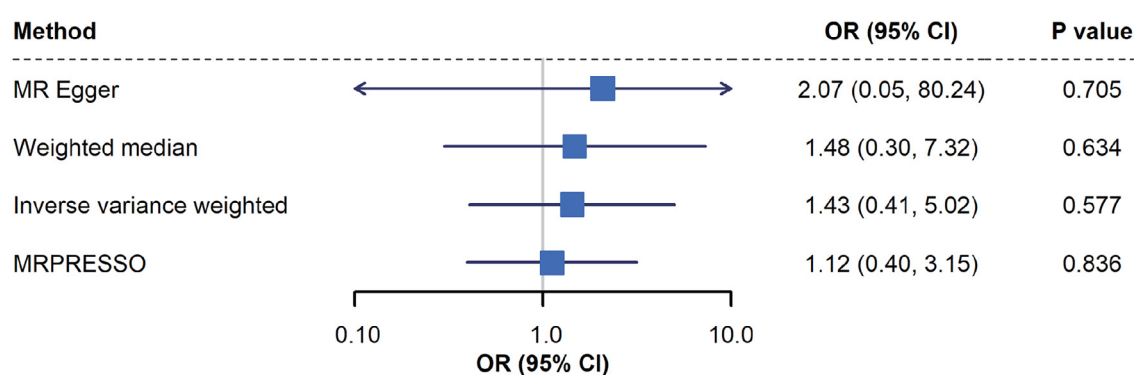
Figure 4. MR analysis shows the causal effect of T2DM and FBP on pancreatic cancer in an east-Asian population.

pancreatic cancer where we compared the absolute and relative incidence of pancreatic cancer in T2DM with the general population. MR analysis further established the potential causality under the positive association between T2DM and pancreatic risk, especially in the east-Asian patients. To the best of our knowledge, this study was the first to investigate both the absolute and relative pancreatic cancer risk across different age groups. Similar to findings shown in a US cohort,[27] the absolute pancreatic cancer risk increased with age in patients with T2DM in the present study. However, the SIRs of pancreatic cancer were inversely related to age at onset of T2DM and a significantly higher SIR of 5·73 was observed in those with onset between 20 and 54 years of age. Cancer trends in these young patients with early onset of T2DM reflect recent changes,[29] which could foreshadow the future overall disease burden. Young-onset T2DM might be an important risk factor for pancreatic cancer and this suggests that close follow-up program for pancreatic cancer should be implemented in this group with early onset of T2DM.

In the cohort of persons with T2DM observed from shortly after the time of diagnosis, there is increased risk of pancreatic cancer during the initial year and then again subsequent to more than 5 years after diagnosis. In a meta-analysis with thirty-five cohort studies, the

highest risk of pancreatic cancer was found among patients diagnosed within less than 1 year.[30] In our large-scale study, we found T2DM patients in the first 1-year duration had lower body mass index and higher glucose levels compared to those in other groups. The relationship between T2DM and pancreatic cancer are complex,[31] while diabetes of ≤ 1 year duration is associated with pancreatic cancer, this could be an early manifestation of pancreatic cancer. In a retrospective cohort study using the UK General Practice Research Database, the incidence of pancreatic cancer was highest in patients with ≥ 5 years duration of T2DM.[32] In our study, we also found T2DM patients diagnosed more than 5 years had the higher risk. Individuals with a long duration of T2DM also have a significantly increased risk of pancreatic cancer, which supports the likelihood of a causal relationship between diabetes and pancreatic cancer. To the best of our knowledge, this is the first report between the risk of pancreatic cancer and diabetes duration in a large-scale T2DM study.

Prospective studies have indicated that elevated blood glucose levels may be linked with increased cancer risk, but the strength of the association is unclear. We found that the risk of pancreatic cancer among patients with FBG ≥ 10·0 mmol/L was 2·35 (95% CI; 1·77-3·13) times greater than in all T2DM patients, 2·25

(95% CI; 1·54−3·29) times in males, and 2·41 (95% CI; 1·56−3·72) times in females respectively, compared to that among those with FBG <6·0 mmol/L. Thus, along with T2DM diagnosed more than 5 years, higher FBG should be considered a risk marker for pancreatic cancer. After assessing the association between FBG categories and risk of pancreatic cancer, we continued to analyze the risk by FBG categories and age at onset categories combined. As expected, we found that the highest incidence of pancreatic cancer (250·25 per 100.000 PYs) was observed in those aged ≥75 years old having FBG ≥ 10·0 mmol/L. The highest SIR of 16·73 (95%CI, 9·37−27·59) was observed in those with age of diagnosis of T2DM 20−54 years having FBG ≥ 10·0 mmol/L. The MR analysis showed increased FBG in the normal range might not increase the risk of pancreatic cancer (p = 0.577). However, when the FBG approached pathological level, which was diagnosed as T2DM, it could significantly worsen the status of pancreas neoplasm (p = 0.001).

This stronger association with highest glucose levels held up over many years and this association reflects a greater severity of metabolic syndrome which would be expected to have some dose relationship with pancreatic cancer risk.[14] Metabolic syndrome and its components have long been investigated as risk factors for pancreatic cancer. Recently, Park et al investigated the association between metabolic syndrome and pancreatic cancer risk in a nationwide Korean cohort from the Korean National Health Insurance System.[33] In this study, recovery from metabolic syndrome was associated with a reduced risk of pancreatic cancer compared with persistent metabolic syndrome, suggesting that pancreatic cancer risk can be altered by changes in metabolic syndrome status. No significant differences by sex or obesity status were observed. The findings from this study highlight the importance of considering both the presence and the changes in the metabolic syndrome when evaluating pancreatic cancer risk. We have attempted to investigate some of these potential mechanisms via multivariate analysis adjusting for age, SBP and BMI, such that FBG ≥10·0 mmol/L continued to be significantly associated with a higher risk of pancreatic cancer than FBG <6·0 mmol/L. The relationship of pancreatic cancer and poor glucose control in T2DM has important implications. Efforts toward early detection and the improvement of glucose metabolism might represent an effective strategy to slow the increasing trend of pancreatic cancer.

The relationship of pancreatic cancer to long diabetes duration and poor glucose control in T2DM has important implications. Efforts toward early detection and the improvement of glucose metabolism might represent an effective strategy to slow the increasing trend of pancreatic cancer. Antidiabetic drugs have been found to have various effects on pancreatic cancer in previous studies. Use of metformin was associated with a significantly decreased risk, while long-term insulin use among patients was associated with a moderately higher risk of pancreatic cancer.[34] Present data do not suggest any association of DPP4i with pancreatic cancer, although they are insufficient to draw definitive conclusions.[35] T2DM is considered a modifiable risk factor for pancreatic cancer in populations of the Asia-Pacific region.[6] With rapid industrialization, urbanization, and westernization of lifestyle, T2DM has increased rapidly in the Chinese population. China has been among the countries with the highest prevalence of T2DM in Asia and has the largest absolute number of T2DM around the world.[7,8] The high prevalence and accelerated epidemic of T2DM has become a major public health challenge and undoubtedly increases the risk of pancreatic cancer. Risk reducing activities could be expected to lead to a significant reduction of this cancer, particularly in China with its very large population.

Our study should be interpreted within the context of its limitations. First, potential risk factors related to pancreatic cancer incidence, such as medication use, smoking history, alcohol consumption, and physical activity were not available from all patients in the current system and were not included in the present analysis, which might exert a bias on the statistical analysis. Second, although all diagnosed cases of T2DM in Shanghai were required to register in the management system, selection bias might exist because the registered T2DM cases were mainly identified through screenings and outpatient visits to community health centers. Elderly people tended to participate in screenings and visit community health centers, while young and middle-aged adults preferred the academic hospitals. However, for total risk evaluation, we used age-standardized rates of pancreatic cancer to avoid the influence of age. Moreover, we used Mendelian randomization (MR) to further validate the results from our observational cohort. This type of study that combines both observational and clinical research with MR has been widely accepted to mutually verify the results.[36,37] However, few previous studies compared the causal effect of fasting plasma glucose (normal range) and type 2 diabetes (abnormal range) on pancreatic cancer, especially in east Asian population.[38,39] Therefore, another novelty of our study is that we firstly extracted instrument variables of fasting plasma glucose and type 2 diabetes from the latest and largest released Asian genome-wide association studies[22,23] to support our observational results.

To the best of our knowledge, this is the largest study in China to investigate the incidence of pancreatic cancer in new-onset T2DM. New-onset T2DM was significantly associated with a higher risk of pancreatic cancer among Chinese adults, which was supported by MR in an east-Asian ancestry population. Young-onset T2DM had notably higher relative risk of pancreatic cancer. Patients with T2DM diagnosed more than 5 years and with elevated FBG levels had increased risk of

pancreatic cancer. Efforts toward early and close follow-up programs, especially in individuals with young-onset T2DM, and the improvement of glucose control might represent effective strategies for improving the detection and results of treatment of pancreatic cancer.

Contributors
B. S., J. T. and Y. S. contributed to the study design. Y. L. and L. L. have accessed and verified the data. T. H. contributed to the Mendelian randomization analysis. C-S.S. and J.T. wrote the manuscript. T. H., Y. P., K. G., C.W., S.S. and X. L. contributed to the discussion of the project. J. C., Y.S., K. H., Z. T. B. and B. S. reviewed and edited the manuscript. All authors participated in critical revision of the manuscript for important intellectual content. B. S., J.T., J. C. and Y. S. were responsible for the decision to submit the manuscript.

Data sharing statement
The data analyzed during the current study are available from the corresponding author on reasonable request.

Declaration of interests
None.

Supplementary materials
Supplementary material associated with this article can be found in the online version at doi:10.1016/j.lanwpc.2022.100596.

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