

# Risk of Diabetes Mellitus after First-attack Acute Pancreatitis: A National Population-based Study

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## Introduction

A recent meta-analysis of 24 prospective studies on patients with first-episode acute pancreatitis (AP) shows that DM develops in 15% within one year and the risk at least doubles over five years after AP (relative risk 2.7, 95% confidence interval [CI] 1.9-3.8). Without a population-based control, the question of whether and to what extent AP increases the risk of DM remains to be answered.

## Methods

### Database

Data in this study were retrieved from Taiwan National Health Insurance Research Database (NHIRD). The study cohort was drawn from a subset of the NHIRD, the Longitudinal Health Insurance Database of 2000 (LHID-2000). The LHID-2000 included one million randomly selected beneficiaries, which represented about 5% of the Taiwanese population enrolled in 2000.

### Definitions and study cohort

AP was defined by ICD-9-CM code 577.0 in any position of the five diagnoses from the inpatient claims data.

Figure 1 shows the process of patient enrollment.

### End-point

We identified the first outpatient or inpatient diagnosis for DM [including ICD-9-CM codes 250, 251.3 (post-surgical hypoinsulinemia) and 251.8 (other specified disorders of pancreatic internal secretion)] between the index dates in 2000 and the last day of 2010 as the study end-point. All the study subjects were followed from the index date to occurrence of end-point, withdrawal from the insurance system, or December 31, 2010, whichever date came first. Subjects with the last two conditions were considered censored in the analysis.

### Statistical analysis

Cox proportional hazard regression models were performed with adjustment for age, sex, income level, geographic area, urbanization, and the Charlson index (continuous variable) to estimate the hazard ratio (HR) of DM in relation to AP. Because both severity and recurrence of AP are associated with increased risk of DM, we repeated the analyses according to the severity and by excluding patients with recurrence (before the diagnosis of DM) after the first-attack (n=823, 27.7%). Finally, we also assessed the risk of DM requiring long-term insulin therapy (ICD codes 250.\*1 and 250.\*3) after mild AP. A two-tailed P value <0.05 was considered statistically significant.

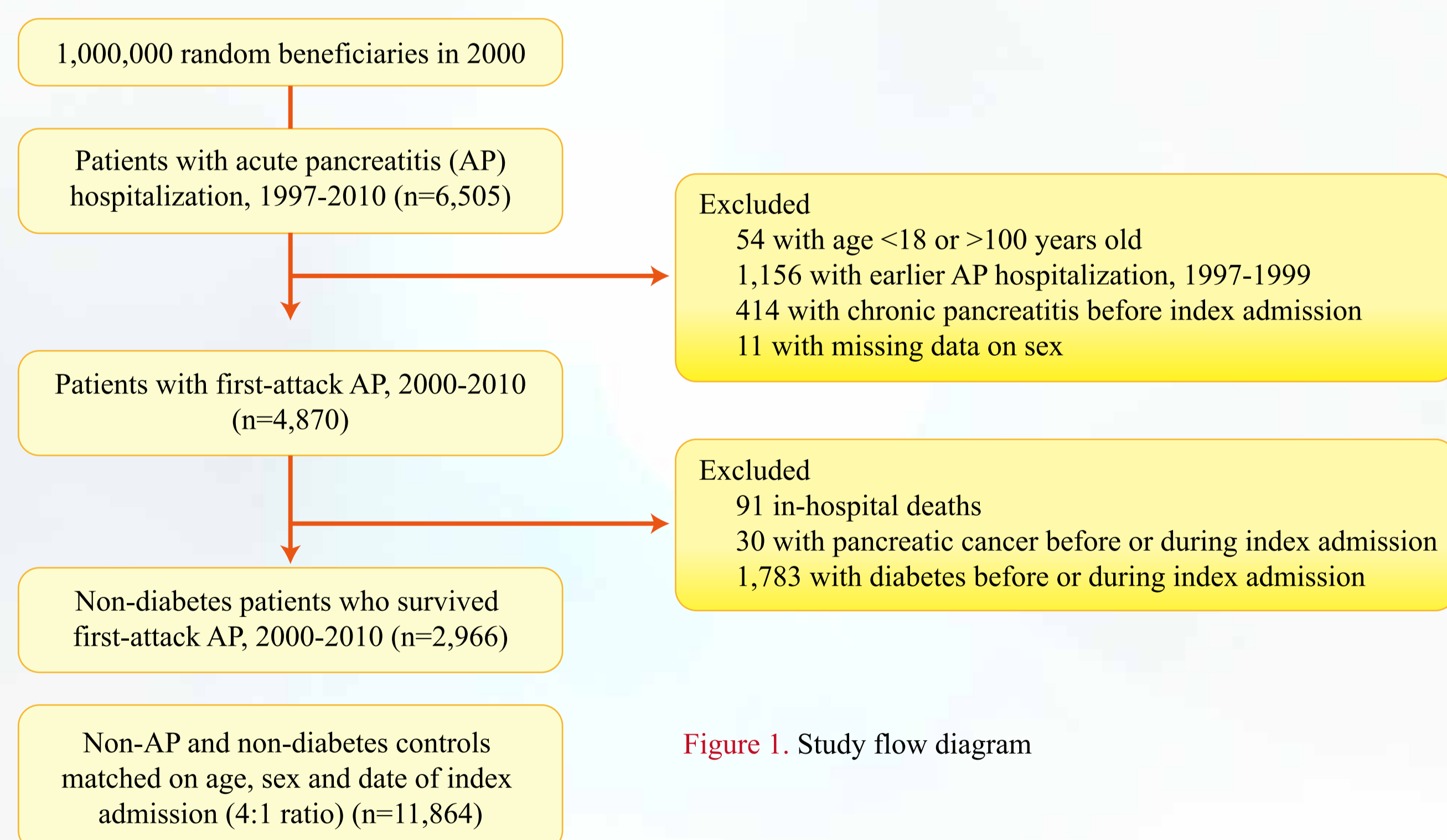


Figure 1. Study flow diagram

## Results

The overall and age- and sex-specific IDs and relative hazards of DM in both groups are shown in Table 2.

Kaplan-Meier failure estimates of DM between the two groups are shown in Figure 2.

Stratified analyses by severity of AP are shown in Tables 3 and 4.

The exclusion of subsequent recurrence of AP only slightly reduced the HRs, but did not change the results (data not shown).

As the endpoint was limited to DM requiring long-term insulin therapy, the overall adjusted HR was 5.05 (95% CI 1.75-14.55) in patients with mild AP. Due to small number of the outcome (n=10), age- and sex-specific analyses were not performed.

Table 1. Characteristics of the study subjects

Variables	Control group (n=11,864)		AP group (n=2,966)		P values
	n	%	n	%	
Mean age (SD), years	51.1 (17.7)		51.1 (17.7)		
18-44	5232	44.1	1303	43.9	
45-64	3715	31.3	931	31.4	
65+	2917	24.6	732	24.7	
Sex					
Female	3656	30.8	914	30.8	
Male	8208	69.2	2052	69.2	
Geographic area*					<0.001
Northern	5506	46.4	1149	38.7	
Central	2736	23.1	837	28.2	
Southern	3174	26.8	799	26.9	
Eastern	315	2.7	128	4.3	
Urbanization*					<0.001
Urban	4944	41.7	983	33.1	
Suburban	3395	28.6	849	28.6	
Rural	3375	28.4	1074	36.2	
Income level*					<0.001
None	2175	18.3	567	19.1	
Low	2004	16.9	663	22.4	
Middle	4341	36.6	1209	40.8	
High	3225	27.2	480	16.2	
Mean Charlson's score (SD)	1.3 (1.8)		2.6 (2.4)		<0.001
0	5400	45.5	376	12.7	
1	2800	23.6	718	24.2	
>=2	3664	30.9	1872	63.1	

\* Inconsistency between the total population and the population added for individual variables was because of missing information. AP: acute pancreatitis; SD, standard deviation.

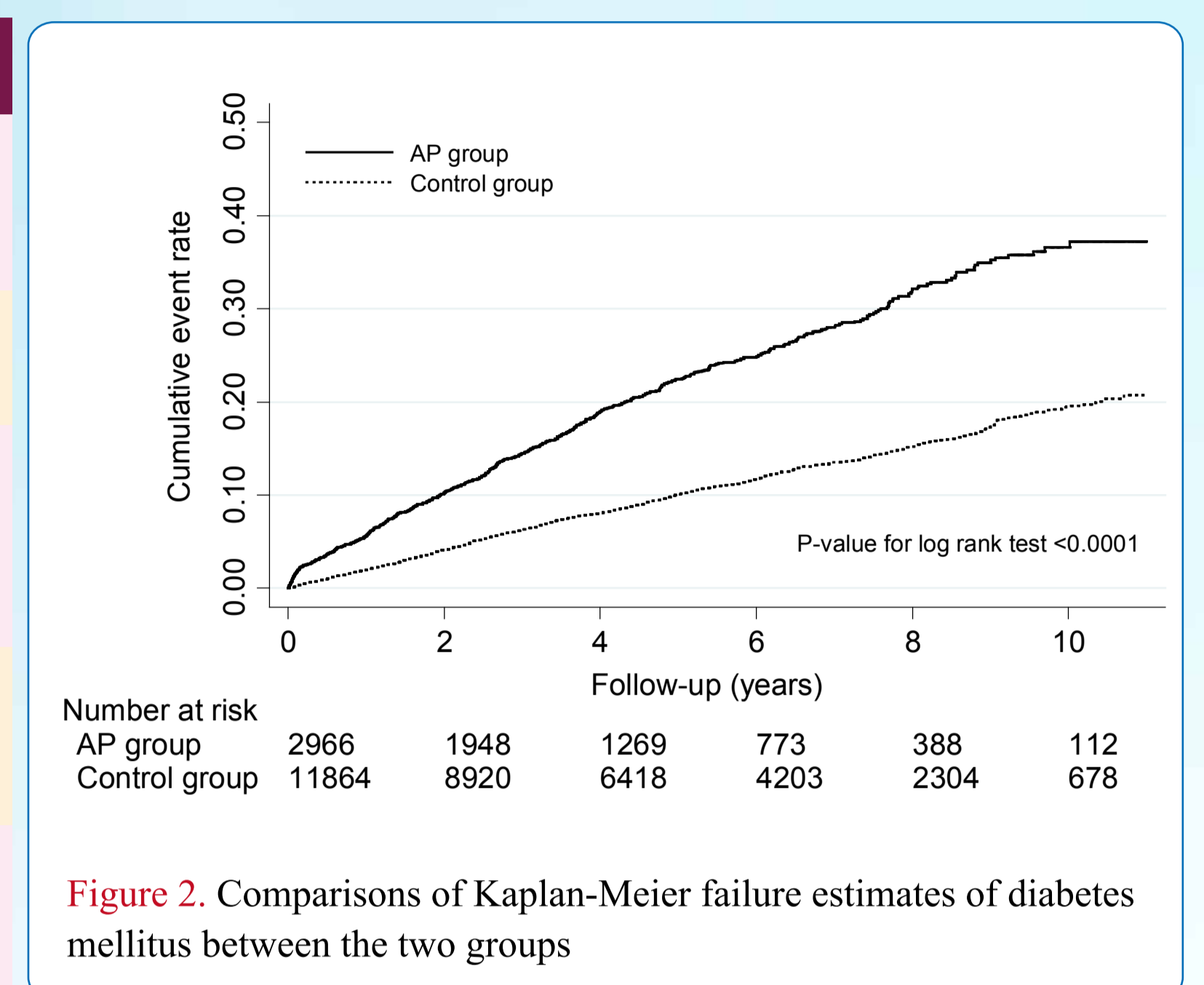


Figure 2. Comparisons of Kaplan-Meier failure estimates of diabetes mellitus between the two groups

Table 2. Overall and age- and sex-specific incidence densities (ID) and relative hazards of diabetes mellitus (DM) in the acute pancreatitis (AP) and control groups.

Variables	Control group			AP			HR (95% CI) <sup>†</sup>	AHR (95% CI) <sup>‡</sup>
	N	DM, n	ID (95% CI)* per 1,000 patient-years	N	DM, n	ID (95% CI)* per 1,000 patient-years		
Men								
<45 years	4137	216	9.8 (8.5-11.2)	1032	230	52.1 (45.5-59.2)	5.33 (4.42-6.42)	4.34 (3.49-5.40)
45-64 years	2433	289	24.6 (21.8-27.6)	607	135	56.7 (47.6-67.2)	2.31 (1.88-2.83)	2.20 (1.76-2.76)
≥65 years	1638	257	43.2 (38.0-48.7)	413	71	54.6 (42.6-68.8)	1.26 (0.97-1.64)	1.22 (0.93-1.60)
Total	8208	762	19.2 (17.8-20.6)	2052	436	53.8 (48.9-59.1)	2.80 (2.49-3.15)	2.46 (2.16-2.80)
Women								
<45 years	1095	52	9.4 (7.0-12.3)	271	30	25.0 (16.9-35.7)	2.66 (1.70-4.18)	2.06 (1.23-3.47)
45-64 years	1282	171	27.8 (23.8-32.3)	324	57	40.9 (31.0-53.0)	1.47 (1.09-1.99)	1.34 (0.98-1.83)
≥65 years	1279	202	41.4 (35.9-47.5)	319	58	57.7 (43.8-74.6)	1.38 (1.03-1.85)	1.32 (0.97-1.79)
Total	3656	425	25.7 (23.3-28.2)	914	145	40.3 (34.0-47.4)	1.56 (1.29-1.89)	1.42 (1.16-1.73)
Overall	11864	1187	21.1 (19.9-22.3)	2966	581	49.7 (45.7-53.9)	2.34 (2.12-2.59)	2.06 (1.85-2.30)

CI=confidence interval; HR=hazard ratio; AHR=adjusted hazard ratio. \* Based on Poisson assumption. †Based on Cox proportional hazard regression with adjustment for age, sex, geographic area, urbanization, income, and Charlson's score. ‡The interactions were statistically significant for AP with sex (β=0.5388, P<0.0001) and with age in men (β=0.6701, P<0.0001), but not for AP with age in women (β=0.2038, P=0.1098).

Table 3. Overall and age- and sex-specific incidence densities (ID) and relative hazards of diabetes mellitus (DM) in mild acute pancreatitis (AP) and control groups.

Variables	Control group			Mild AP group			HR (95% CI) <sup>†</sup>	AHR (95% CI) <sup>‡</sup>
	N	DM, n	ID (95% CI)* per 1,000 patient-years	N	DM, n	ID (95% CI)* per 1,000 patient-years		
Men								
<45 years	3493	187	10.1 (8.7-11.7)	870	192	50.7 (43.8-58.4)	5.04 (4.12-6.17)	4.20 (3.33-5.29)
45-64 years	1946	240	25.0 (21.9-28.4)	487	106	52.6 (43.1-63.6)	2.11 (1.68-2.65)	2.03 (1.58-2.61)
≥65 years	1165	182	43.1 (37.1-49.9)	294	51	54.5 (40.5-71.6)	1.27 (0.93-1.73)	1.24 (0.90-1.71)
Total	6604	609	18.8 (17.4-20.4)	1651	349	51.8 (46.5-57.5)	2.75 (2.41-3.13)	2.46 (2.13-2.84)
Women								
<45 years	937	49	10.3 (7.6-13.6)	233	26	24.6 (16.1-36.1)	2.41 (1.50-3.87)	1.89 (1.09-3.29)
45-64 years	1113	156	28.8 (24.5-33.7)	280	45	35.4 (25.8-47.3)	1.23 (0.88-1.72)	1.12 (0.79-1.58)
≥65 years	998	155	39.6 (33.6-46.3)	249	43	51.6 (37.3-69.5)	1.30 (0.93-1.82)	1.26 (0.88-1.80)
Total	3048	360	25.5 (22.9-28.3)	762	114	36.1 (29.7-43.3)	1.41 (1.14-1.74)	1.27 (1.02-1.59)
Overall	9652	969	20.9 (19.6-22.2)	2413	463	46.8 (42.6-51.2)	2.24 (2.00-2.50)	1.99 (1.76-2.24)

CI=confidence interval; HR=hazard ratio; AHR=adjusted hazard ratio. \* Based on Poisson assumption. †Based on Cox proportional hazard regression with adjustment for age, sex, geographic area, urbanization, income, and Charlson's score. ‡The interactions were statistically significant for AP with sex (β=0.6411, P<0.0001) and with age in men (β=0.6641, P<0.0001), but not for AP with age in women (β=0.1885, P=0.1858).

Table 4. Overall and age- and sex-specific incidence densities (ID) and relative hazards of diabetes mellitus (DM) in severe acute pancreatitis (AP) and control groups.

Variables	Control group			Severe AP group			HR (95% CI) <sup>†</sup>	AHR (95% CI) <sup>‡</sup>
	N	DM, n	ID (95% CI)* per 1,000 patient-years	N	DM, n	ID (95% CI)* per 1,000 patient-years		
Men								
<45 years	644	29	8.2 (5.5-11.8)	162	38	60.3 (42.7-82.8)	7.24 (4.45-11.78)	5.29 (2.74-10.22)
45-64 years	487	49	22.8 (16.9-30.1)	120	29	79.5 (53.3-114.2)	3.57 (2.25-5.68)	3.28 (1.93-5.59)
≥65 years	473	75	43.2 (34.0-54.2)	119	20	54.9 (33.5-84.7)	1.22 (0.75-2.00)	1.18 (0.71-1.98)
Total	1604	153	20.7 (17.5-24.2)	401	87	64.0 (51.3-78.9)	3.05 (2.34-3.97)	2.42 (1.80-3.26)
Women								
<45 years	158	3	4.0 (0.8-11.6)	38	4	27.8 (7.6-71.2)	7.09 (1.58-31.75)	4.36 (0.59-32.16)
45-64 years	169	15	20.5 (11.5-33.8)	44	12	98.2 (50.7-171.5)	4.59 (2.13-9.91)	5.53 (2.15-14.25)
≥65 years	281	47	49.0 (36.0-65.2)	70	15	87.7 (49.1-144.6)	1.65 (0.92-2.97)	1.55 (0.85-2.86)
Total	608	65	26.6 (20.5-33.9)	152	31	70.9 (48.2-100.6)	2.49 (1.62-3.82)	2.34 (1.46-3.74)
Overall	2212	218	22.1 (19.3-25.3)	553	118	65.7 (54.4-78.7)	2.88 (2.30-3.61)	2.40 (1.87-3.07)

CI=confidence interval; HR=hazard ratio; AHR=adjusted hazard ratio. \* Based on Poisson assumption. †Based on Cox proportional hazard regression with adjustment for age, sex, geographic area, urbanization, income, and Charlson's score. ‡The interactions were statistically significant for AP with age in men (β=0.7562, P<0.0001), but not for AP with sex (β=0.0545, P=0.8332) or for AP with age in women (β=0.6087, P=0.0598).

## Conclusions

This is the first population-based study to demonstrate a two-fold increase of DM after first-attack AP. Results of this study would provide valuable information for physicians and patients on the need and guidance of long-term follow-up for the development of DM after first-time AP attack.