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New-Onset Diabetes Mellitus After the First Attack of Acute Pancreatitis: A Systematic Review and Meta-Analysis

Qiu Ping Liu [#2], Cun Liang Hu [#1] and Ni Wei Chen [1, *]

[1]Department of Gastroenterology, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Shanghai, China
[2]Department of Respiratory Medicine, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Shanghai, China

[*]*Corresponding author*: Department of Gastroenterology, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, 600 Yishan Road, 200233, Shanghai, China. Email: chenniwei@163.com
#These authors are contributed equally as the first author.

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Abstract

Context: New-onset diabetes mellitus (DM) after the first attack of acute pancreatitis (AP) has not been fully elucidated.
Objectives: The study aimed to explore the incidence and time-course of pancreatic endocrine insufficiency in patients with new-onset prediabetes or DM after the first attack of AP.
Data Sources: A comprehensive literature review was conducted by searching four major biomedical journal databases (PubMed, Embase, Cochrane Library, and Web of Science).
Study Selection: We included all prospective clinical studies that investigated the change in the metabolization of glucose after hospital discharge following the first attack of AP.
Data Extraction: After quality assessment, data were extracted according to a standard protocol. Because of between-study heterogeneity, data were analyzed by the random-effects method.
Results: The inclusion criteria were met by 12 clinical studies, including 766 patients with the first attack of AP. Prediabetes and/or DM was observed in 51% (95% CI: 55% to 63%) of the patients after the first attack of AP. The pooled incidence of prediabetes and DM after AP was 23% (95% CI: 16% to 30%) and 18% (95% CI: 11% to 26%), respectively. The risk of new-onset prediabetes and DM significantly increased in 1 - 3 years (relative risk (RR): 4.00 (95% CI: 1.68 - 9.53)) and 3 - 5 years (RR: 2.12 (95% CI: 1.9 - 3.8)), respectively.
Conclusions: New-onset prediabetes and/or DM after the first attack of AP developed in 51% of the patients after hospital discharge and the risk of DM increased more than two folds over three years.

Keywords: Acute Pancreatitis, Diabetes Mellitus, Exocrine Pancreatic Insufficiency, Glucose, Incidence, Islets of Langerhans, Meta-Analysis, New-Onset, Pancreatic Diseases, Prediabetic State

1. Context

Diabetes mellitus (DM) is a metabolic disease with a globally increasing prevalence. In 2015, 30.2 million people (9.4%) of the US population had diabetes (1). Diabetes is the seventh leading cause of death in the United States (1). DM is a risk factor for various diseases including coronary heart disease (2), stroke (3), kidney failure (4), lower limb ischemia (5), blindness (6), amputations of the legs and feet (7), and even early death. As for the health and economic perspective, DM is a life-threatening disease, affecting millions of people around the world every year and imposing a large economic burden, with high treatment cost. Prediabetes is a warning sign that people are on the path of diabetes. Impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) are the two forms of prediabetes. The burden of prediabetes is similar to that of DM. The USA estimated 84.1 million US adults with prediabetes in 2015 (1). It is the predisposing stage before DM in which people are more likely to develop diabetes (1, 8-10). About 20% of patients with prediabetes progress to diabetes over five years (8). Moreover, the global burden of prediabetes and DM is expected to increase as the population ages, and nonfatal outcomes require more resources from health care systems. Hence, prevention, and timely diagnosis of prediabetes and DM have important implications. Screening of individuals at high risk of developing DM is needed to identify patients with prediabetes and take measurements to prevent the beginning of DM (11).

Acute pancreatitis (AP) is the most common pancreatic disease (12), with a prevalence reported from 17 countries across Europe, ranging from 4.6 to 100 per 100,000 population (13). It is an acute inflammatory disease of the pan-

creas characterized by a sudden onset of upper abdominal pain, nausea, emesis, and increased pancreatic digestive enzymes in the serum and urine. Impaired function of the endocrine pancreas causes prediabetes or DM (14). It is generally believed that hyperglycemia can completely recover in most patients after AP. That is why glucose metabolism is not continually measured after leaving the hospital. However, some studies demonstrated that hyperglycemia persists in a proportion of patients after AP (15, 16). Therefore, it is necessary to clarify the time course of prediabetes and DM after the first attack of AP.

There is one published meta-analysis (17) investigating the association between new-onset DM and the first attack of AP. In recent five years, new studies have demonstrated the occurrence of new-onset DM after the first attack of AP. Furthermore, the incidence of DM after AP has changed over recent years. Therefore, it is important to estimate the new-onset DM after the first attack of AP again.

The aim of the study was to perform a systematic review and meta-analysis of studies reporting the incidence and time course of new-onset prediabetes and/or DM after the first attack of AP.

2. Objectives

The study aimed to explore the incidence and time course of pancreatic endocrine insufficiency in patients with new-onset prediabetes or DM after the first attack of AP.

3. Data Sources

We performed a search to evaluate all prospective clinical trials that investigated the change in the metabolization of glucose after hospital discharge following the first attack of AP. We searched four major databases (PubMed, Embase, Cochrane Library, and Web of Science) from the time of inception (1946 for PubMed, 1980 for Embase, 1980 for Cochrane Library, and 1980 for Web of Science) until October 2018. The search strategy used was as follows:

"acute pancreatitis" AND ("diabetes mellitus" OR "type 2 diabetes mellitus" OR "type 1 diabetes mellitus" OR "non-insulin dependent diabetes mellitus" OR "insulin- dependent diabetes mellitus" OR "prediabetic state" OR "impaired glucose tolerance" OR "impaired fasting glucose" OR "impaired glucose regulation").

The references of all the included studies were also searched for other relevant articles. Open Grey and ClinicalTrials.gov were also searched. The search was limited to publications in English.

4. Study Selection

The criteria for including studies are in the following: (1) prospective clinical human studies; (2) patients aged > 18 years experiencing the first attack of AP; (3) reporting diagnostic laboratory testing for pancreatic endocrine insufficiency, and (4) at least one-month follow-up time after hospital discharge.

Studies were excluded if any of the following existed: (1) patients had pre-existing DM or prediabetes, or studies did not state whether patients had pre-existing DM or prediabetes; (2) patients performed pancreatic surgery (such as necrosectomy or pancreatic resection), and (3) patients with autoimmune, chronic or hereditary pancreatitis and gestational diabetes.

5. Data Extraction

To ensure accuracy, two authors (CunLiang Hu and QiuPing Liu) independently performed data extraction, study selection, and quality assessment and a senior author (NiWei Chen) reviewed the process. Disagreements were resolved by discussion between the two authors and the senior author. The following information was obtained from each selected study: (1) study/author, (2) country, (3) study design, (4) follow-up time, (5) severity of AP, (6) endocrine function tests, (7) the number of patients under endocrine assessment, (8) the number of multiple attacks of AP at follow-up, (9) prediabetes/DM after AP, (10) diabetic diet and physical exercise, DM treated with oral diabetes drugs, and DM treated with insulin after AP, (11) total individuals studied, (12) age, (13) the proportion of male to female patients, (14) body mass index (BMI), (15) etiology of AP (biliary, hyperlipemia, alcohol, other), (16) the number of participating centers, and (17) criteria used to diagnose AP and classify its severity. The corresponding authors were contacted if necessary.

5.1. Quality Assessment

We used the Newcastle-Ottawa Scale (NOS) to evaluate the quality of eligible studies (18). According to the three aspects of research design (patient selection, comparability of research groups, and exposure/outcomes of research participants), it allocates up to nine points to each study. If the score is 5 or more, the quality of research is considered high; if the score is less than 5, the quality of research is considered low (19).

5.2. Definitions

AP is defined as having two of the following three items: (1) abdominal pain characteristic of AP, (2) serum

amylase and/or lipase three times the upper limit of normal, and (3) AP characteristic findings on computed tomography (20). Fasting blood glucose (FBG) and/or 2-h oral glucose tolerance test (OGTT) were used to define prediabetes and DM. IFG is defined as FBG $\geq$ 5.6 mmol/L and < 7.0 mmol/L, or $\geq$ 6.1 mmol/L and < 7.0 mmol/L. IGT is defined as 2-h OGTT $\geq$ 7.8 mmol/L and < 11.1 mmol/L. Diabetes is defined by typical diabetes symptoms with any of the following items: (1) FBG $\geq$ 7.0 mmol/L, (2) random blood glucose $\geq$ 11.1 mmol/L, and (3) 2-h OGTT $\geq$ 11.1 mmol/L (21, 22).

5.3. Data Processing and Statistical Analysis

The pooled prevalence for each of the outcomes was calculated. Random-effects model, pooled prevalence, and associated 95% confidence intervals (CIs) were used to evaluate pancreatic endocrine dysfunction. R console version 3.5.1 was used to perform forest plot analysis, funnel plot analysis, sensitivity analysis, subgroup analysis, and meta-regression analysis. Between-study heterogeneity in different subgroups was tested using the I^2-statistics. The I^2 values of < 25%, 25% - 50%, 50% - 75%, and $\geq$ 75% were classified as low, moderate, high, and very high heterogeneity, respectively (23). Egger's test was used to assess publication bias. Sensitivity analyses were limited to studies that used the 1999 WHO definition of DM and studies with SAP. Subgroup analysis was performed to find a possible change in pancreatic endocrine dysfunction over time by comparing studies of different follow-up periods (up to 12 months, 12 - 36 months, 36 - 60 months, and more than 60 months). Meta-regression analysis was conducted to explore whether sex, age, follow-up time, and etiology of AP (proportion of biliary, hyperlipemia, alcohol, other etiology) had an important impact on prognosis. The review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (24).

6. Results

6.1. Study Characteristics

The search retrieved a total number of 4834 studies of which, 65 relevant papers were included in the assessment. Finally, 12 studies were used in the analysis (Figure 1) (16, 25-35). Cohen's kappa coefficient was 0.773 (95% CI: 0.610 - 0.936), which indicates a strong consistency. Table 1 lists the characteristics of the included studies. The included studies recruited 766 AP patients in total (Table 2). All the studies performed prospective cohorts. Eight studies (16, 27, 29, 30, 32-35) were conducted in Europe, three (25, 26, 31) in Asia, and one (28) in South America. All studies were conducted in single centers.

6.2. Quality of Studies

Using the NOS, we assessed the quality of the included studies (Table 3) (18). All of the 12 studies had high quality.

6.3. Publication Bias

Publication bias was examined and there was no evidence of funnel plot asymmetry for DM studies with a P value of 0.09 (Egger's test). Because the number of included studies was less than 10 for prediabetes and/or DM and prediabetes studies, we did not assess the publication bias for them.

6.4. Prediabetes and/or Diabetes

There were eight studies reporting on prediabetes and/or DM after AP (25-28, 30, 33-35), with 517 patients included. The pooled prevalence of prediabetes and/or DM was 51% (95% CI: 41% to 63%), with high statistical heterogeneity between studies (I^2 = 82%). Table 4 and Figure 2A show the time course of prediabetes and/or DM in the included studies.

6.5. Prediabetes

All the eight studies (25-28, 30, 33-35) reported on new-onset prediabetes after AP, comprising 571 patients with a pooled prevalence of 23% (95% CI: 16% to 30%). There was moderate statistical heterogeneity between studies (I^2 = 69%) (Figure 3A). Sensitivity analysis in individuals with severe AP (SAP) included two studies (28, 35), with 38 patients involved. The pooled prevalence of prediabetes was 31% (95% CI: 11% to 90%) and heterogeneity between the studies did not decrease (I^2 = 77%). Sensitivity analysis involved studies that used the 1999 WHO definitions (21), including three studies (25, 26, 33) with 415 patients. The pooled prevalence was 28% (95% CI: 24% to 33%), with no statistical heterogeneity between studies (I^2 = 0%). Subgroup analysis involved follow-up time as shown in Table 2. The prevalence of prediabetes after AP stayed within the range of 13% - 50% and the relative risk of developing prediabetes at any time-point compared to up to 12 months initially decreases with time (Table 4). Time-course analysis of the prevalence of prediabetes is presented in Figure 2B.

6.6. Diabetes Mellitus

There were 11 studies (16, 25-30, 32-35) reported on new-onset DM. They included 707 patients with a pooled diabetes prevalence of 18% (95% CI: 11% to 26%). There was high statistical heterogeneity between studies (I^2 = 82%) (Figure 3B). Sensitivity analysis included individuals with SAP in three studies (28, 32, 35) involving 707 patients. The pooled prevalence of DM in patients with SAP was 26% (95% CI: 16% to 41%), with decreased heterogeneity between the studies

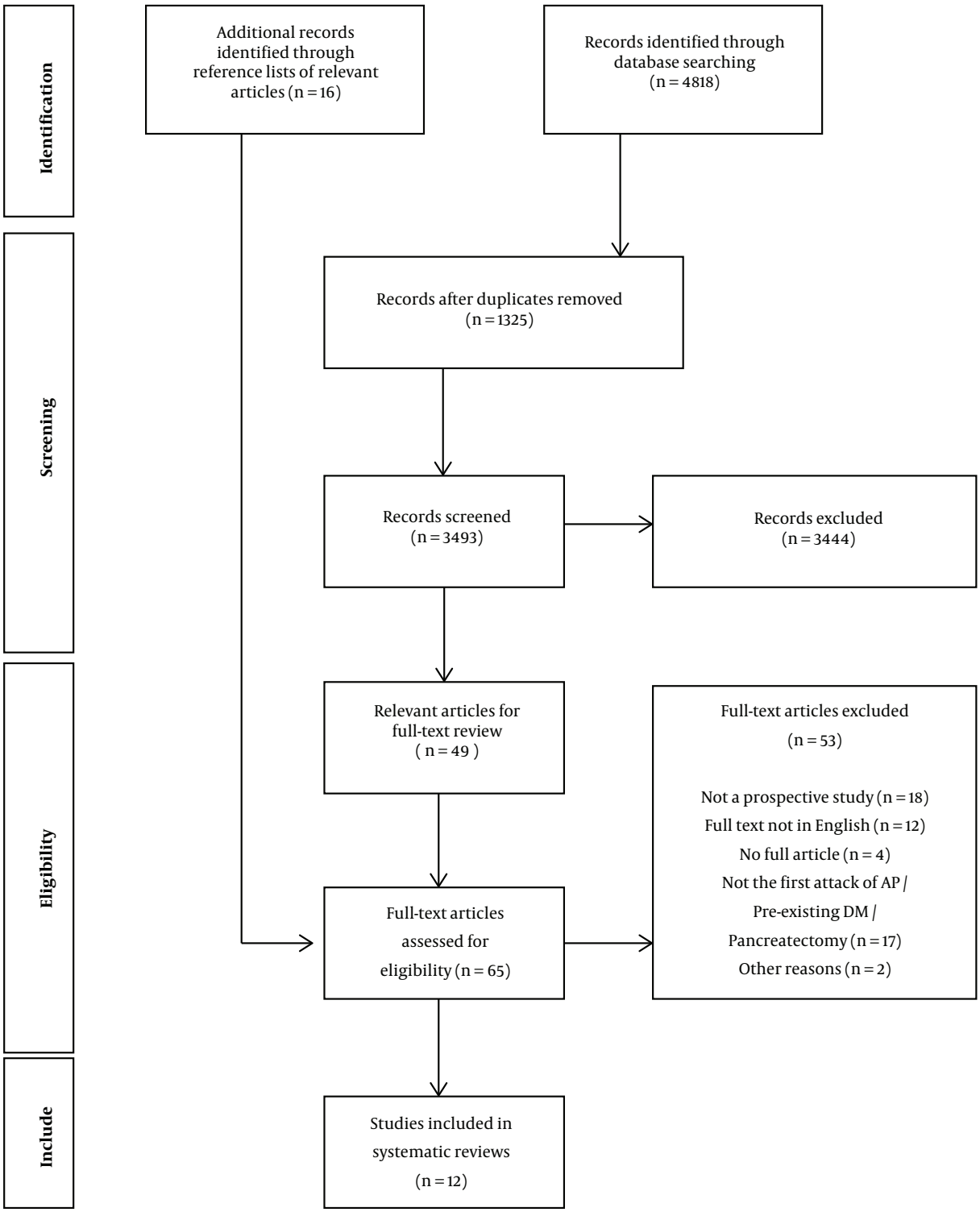

Figure 1. Flowchart of the study selection process

Table 2. Baseline Characteristics of the Included Studies[a]

Study	Year	Total Individuals Studied, No.	Age, y	Gender		BMI, kg/m^2	Etiology			
				Male	Female		Biliary	Hyperlipemia	Alcohol	Other
Tu (25)	2018	256	55	168 (65.6)	88 (34.4)	Not stated	147 (57.5)	88 (34.5)	7 (2.7)	14 (5.3)
Tu (26)	2017	113	46	75 (66.4)	38 (33.6)	< 18.5 (4.4% of patients)	65 (57.5)	39 (34.5)	3 (2.7)	6 (5.3)
Nikkola (27)	2017	77	48	69 (90)	8 (10)	27.7	Not stated	Not stated	Not stated	Not stated
Winter Gasparoto (28)	2015	16	48	9 (56.2)	7 (43.8)	Not stated	10 (62.5)	2 (12.5)	4 (25.0)	0
Vujasinovic (29)	2014	100	56.5	65 (65.0)	35 (35.0)	No stated	36 (36.0)	6 (6.0)	42 (42.0)	16 (16.0)
Nikkola (30)	2013	18	47	18 (100)	0	29.6	0	0	18 (100)	0
Wu (31)	2011	59	58.8	33 (56)	26 (44)	23.2	42 (71)	7 (12)	7 (12)	3 (5)
Uomo (32)	2010	40	63.5	17 (42.5)	23 (57.5)	one:29; another: 32	28 (70.0)	5 (12.5)	0	7 (17.5)
Pelli (33)	2009	54	49	47 (87.0)	7 (13.0)	27	54 (100)	0	0	0
Boreham (16)	2003	23	55	13 (56.6)	10 (43.4)	Not stated	13 (56.6)	1 (4.3)	5 (21.7)	4 (17.4)
Ibars (34)	2002	63	62.3	17 (27)	46 (73)	Not stated	63 (100)	0	0	0
Doepel (35)	1993	37	52	25 (67.6)	12 (32.4)	Not stated	3 (8.1)	0	28 (75.7)	6 (16.2)

Abbreviation: BMI, body mass index.
[a]Values are expressed as No. (%) unless otherwise indicated.

(I^2 = 26%). Sensitivity analysis involved studies that used the 1999 WHO definitions, including three studies (25, 26, 33) with 415 patients. The pooled prevalence was 28% (95% CI: 24% to 33%), with no heterogeneity between the studies (I^2 = 0%). Subgroup analysis, according to the follow-up time, is shown in Table 2. The prevalence of DM after AP remained within the range of 13% - 27%. There was a 2.12-fold increased risk of new-onset DM at 36 - 60 months, which was statistically significant (Table 4). Time-course analysis of the prevalence of DM is presented in Figure 2C.

6.7. Treatment of DM

Limited studies described the treatment of DM (including diabetic diet, physical exercise, treatment with oral diabetes drugs, and treatment with insulin); thus, we did not assess the pooled prevalence of them.

6.8. Meta-Regression Analysis

Meta-regression was performed using the following moderators: age, follow-up time, the proportion of males, the proportion of biliary etiology, the proportion of hyperlipemia etiology, the proportion of alcohol etiology, the proportion of other etiologies, and the total number of patients. The analysis showed that the prevalence of prediabetes and/or DM, prediabetes, and DM was not significantly influenced by these factors (Table 5).

7. Conclusions

We systematically evaluated all 12 available clinical studies reporting on patients with prediabetes and/or DM after the first attack of AP who had been discharged from the hospital. The pooled prevalence of prediabetes and/or DM after AP was 51% while prediabetes and DM were observed in 23% and 18% of the individuals after AP, respectively. Furthermore, the occurrence of prediabetes or DM after AP was more frequent when pancreatitis was more severe; such patients had a higher prevalence of both prediabetes (31%) and DM (26%). The meta-regression analysis indicated that the risk of prediabetes or DM after AP was irrespective of patients' age, gender, etiology, the total number of patients, and follow-up duration. The results also indicated that prediabetes and DM appeared very early after AP. The prevalence of prediabetes and DM after AP was 13% for both in the first 12 months. Unfortunately, no study in this review followed patients with prediabetes to confirm whether they developed DM, but studies proposed that patients with prediabetes are more likely to develop DM (1, 8-10). Compared to the previous meta-analysis (17), we found that the prevalence of new-onset DM after the first attack of AP increases from 37% to 51%. Hence, closer follow-ups of patients after AP, screening of patients with prediabetes, and taking measures to prevent the beginning of DM are necessary.

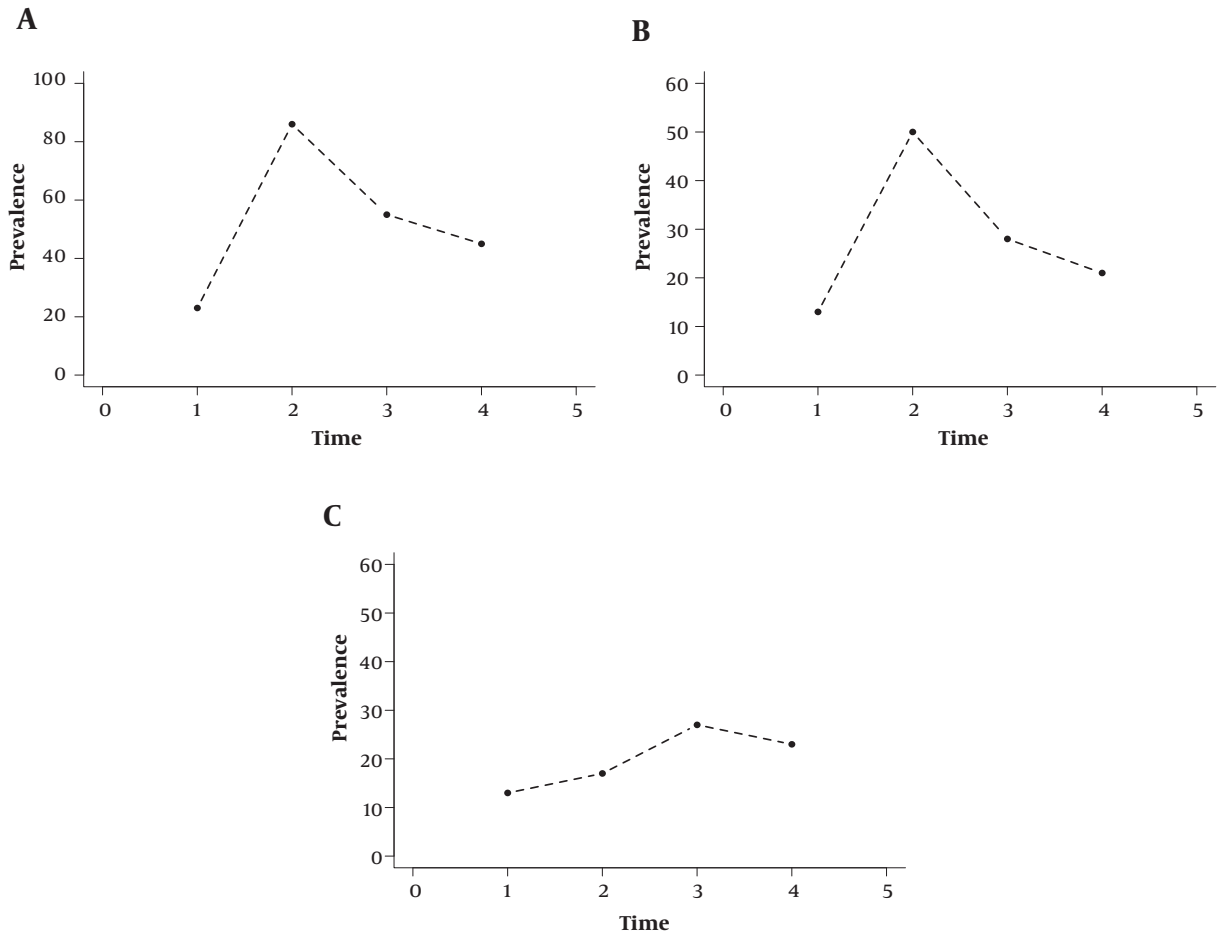

Figure 2. The pooled prevalence of pancreatic endocrine insufficiency with time after the first attack of AP

Table 5. Results of Meta-Regression Analysis[a]

Age	P Values for the Covariates Tested							
		Follow-up Time	Male, %	Biliary, %	Hyperlipemia, %	Alcohol, %	Other Etiologies, %	Total No. of Patients
Prediabetes and/or diabetes mellitus	0.08	0.47	0.20	0.55	0.28	0.37	0.36	0.38
Prediabetes	0.17	0.77	0.37	0.49	0.28	0.42	0.91	0.41
Diabetes mellitus	0.15	0.62	0.12	0.98	0.16	0.47	0.55	0.73

[a]Some covariates unavailable were excluded from the model.

Pancreatogenic DM is an acknowledged condition classified as type 3c diabetes (36-38). Pancreatic necrosis can lead to a decline in the number of β-cell and insulin secretion, known to be the main reason for DM development after AP. The pooled prevalence of prediabetes or DM in patients with SAP was 31% and 26%, respectively. Hence, patients with SAP are more likely to develop prediabetes or DM. First, patients with SAP suffer from a larger decrease in β-cell shortly, with more loss of functional reserve capacity of the gland (15, 16, 26). Second, compared to mild acute pancreatitis (MAP) and moderately severe acute pancreatitis (MSAP), SAP patients with a higher percentage of necrosis are more likely to perform necrosectomy (39), with more number of β-cell decrement. Third, some metabolic factors, such as obesity and hypertriglyceridemia as the risk factors for SAP, contribute to prediabetes or DM after

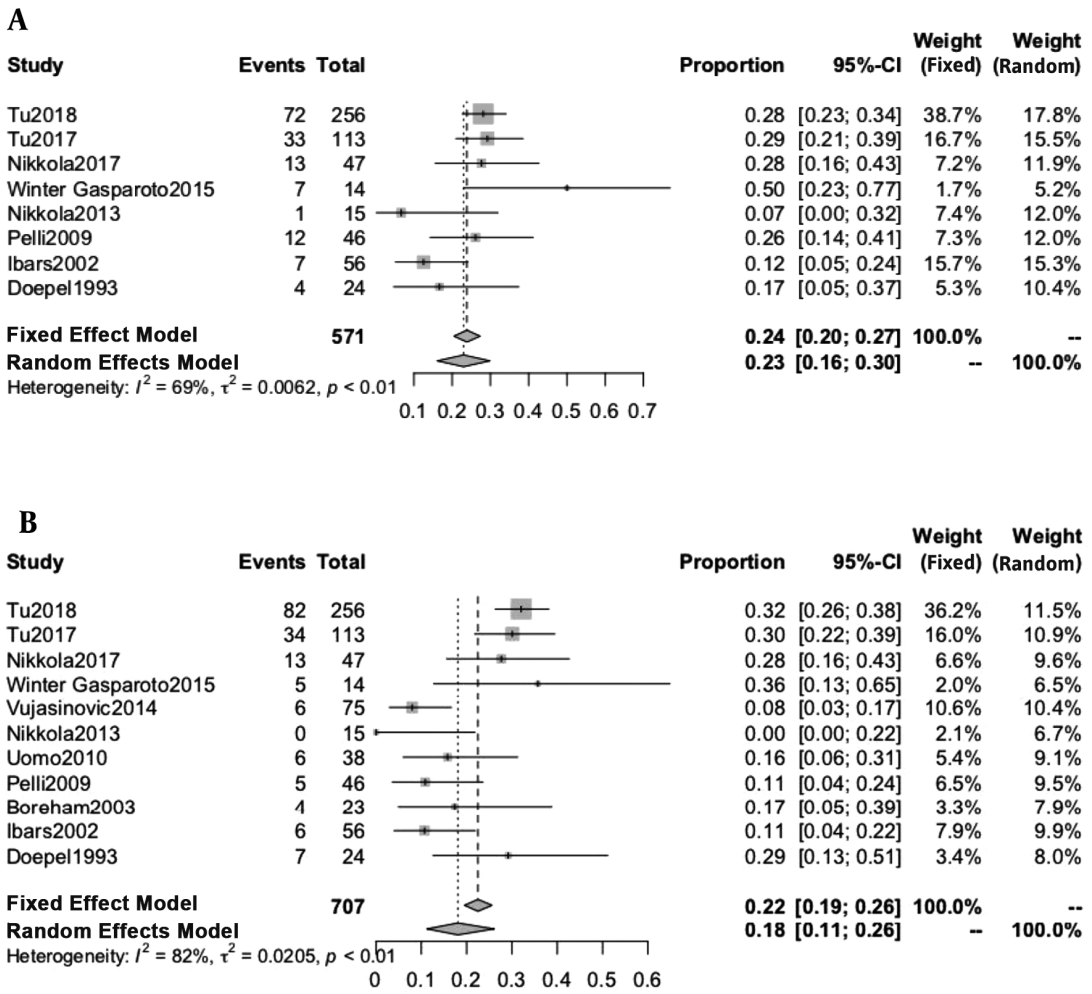

Figure 3. The pooled prevalence of pancreatic endocrine insufficiency after the first attack of AP

AP (40-44). It is also worth mentioning that pre-existing DM itself places individuals at greater risk of developing DM after AP (1, 9). This review excluded patients undergoing necrosectomy and pre-existing DM.

We showed an increasing trend in the prevalence of prediabetes and diabetes as follow-up time increases. Age and recurrent attacks of AP during the follow-up time may have effects on this trend. However, meta-regression analysis showed that age was not a significant influencing factor. Unfortunately, just four studies reported recurrent attacks of AP and only one study made a specific notion of recurrent attacks. Due to insufficient data, this was not analyzed here in this study. Remarkable is that the highest prevalence of prediabetes and diabetes occurred in 1 - 3 years and 3 - 5 years after AP, respectively; however, it decreased thereafter. The question is that did part of prediabetes decreases turn into diabetes? Unfortunately, no study in this review followed patients with prediabetes to confirm whether they developed DM. Most importantly, the prevalence of prediabetes and diabetes decreased after 3 and 5 years of follow-up, respectively. The change in increasing and decreasing trends in the prevalence over time between prediabetes and DM is worthy of attention. It suggests that the human endocrine pancreas has a certain regenerative capacity after acute pancreatitis. This is supported by human and animal experimental models (45). The possibility that pancreatic endocrine function changes with time after acute pancreatitis deserves doctors' attention in the long-term follow-up of acute pancreatitis.

The advantage of this systematic review is that we followed a comprehensive strategy allowing to include all 766 individuals with the first attack of AP after hospital dis-

charge from prospective studies. Open Grey and ClinicalTrials.gov were also searched. Patients with pre-existing DM and pancreatic surgery were excluded, allowing to report new-onset prediabetes and DM after AP accurately. Furthermore, we contacted authors for missing data or unreported variables. By doing so, we included two more studies (25, 29). Statistical analysis is robust when the random-effects model is used to provide the most conservative estimates. We also conducted sensitivity and subgroup analyses (in order to explore possible grounds for statistical heterogeneity) and meta-regression (in order to evaluate the effect of potential confounders).

Attention should be paid to the limitations of this study. First, the high heterogeneity between studies, found in sensitivity and subgroup analyses, limited between-study comparability and indicated that meta-analysis results should be interpreted with caution. Differences in pancreatic endocrine function assessment methods, study designs, and geographical locations may have been the causes of high heterogeneity. Second, there were limited studies in sensitivity analysis and subgroup analysis. Hence, the results of these analyses also should be interpreted with caution. Third, not all studies mentioned BMI, recurrent AP, and DM treatment. Due to insufficient data, it was impossible to explain the impact of these factors. Fourth, the results of the time adjustment analysis should be carefully explained. Our data came from multiple studies with different follow-up times, rather than longitudinal studies with repeated measurements at different time-points. A prospective study of a large cohort of patients over several years is more appropriate for this purpose. Fifth, although this study excluded patients who underwent surgery, they may be included because some studies did not mention surgery information. It has been reported that distal pancreatectomy puts AP patients at a higher risk of DM (46). Sixth, by excluding non-English studies, language bias may have existed. Finally, the management of AP after discharge from the hospital may affect pancreatic endocrine function but, due to insufficient data, this possible confounding factor could not be adjusted for.

We hope to provide some suggestions for future studies on endocrine dysfunction in AP follow-up. First, studies need to declare whether patients had pre-existing DM or underwent necrosectomy. Second, the severity of the disease should be well described, preferably classified according to recognized diseases (e.g., the revised Atlanta Classification (47)). Moreover, BMI, recurrent AP, and DM treatment should also be mentioned in future studies. The consequences of pancreatic endocrine insufficiency may be a major burden on AP patients' lives. Doctors should know which patients are at risk.

In conclusion, this systematic literature review confirms that prediabetes and DM are common after the first attack of AP. It is also suggested that pancreatic endocrine function recovers with time after AP; hence, a formal follow-up of patients after AP is important. Further research should pay more attention to the pathogenesis, detection, and screening of prediabetes/DM after the first attack of AP.

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Footnotes

Authors' Contribution: Cun Liang Hu and Qiu Ping Liu acquired data, drafted the manuscript, acquired data, carried out data analysis, and drafted the manuscript; Ni Wei Chen conceived and supervised the study.

Conflict of Interests: The authors declare that they have no conflicts of interest.

Ethical Considerations: This study do not need ethical considerations.

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Table 1. Characteristics of the Included Studies

Study	Year	Country	Study Design	Follow-up Time (Mean Unless Specified), mo	Severity of Acute Pancreatitis, %	Test of Endocrine Function Used	Total No. of Individuals Undergoing Endocrine Assessment	Presence of Multiple Attacks of AP at Follow-up, %	Prediabetes, %	DM, %	Diabetic Diet and Physical Exercise, %	DM Treated with Oral Diabetes Drugs, %	DM Treated with Insulin, %
Tu (25)	2018	China	Prospective cohort	42.93	MAP 54 (21), MSAP 42 (16.4), SAP 160 (62.5)	OGTT (FBG, 2hPG), FINS, HBA1c, HOMA-β, HOMA-IR	256	Not stated	IGT 72 (28.1) (from author)	82 (32.0) (from author)	Not stated	Not stated	Not stated
Tu (26)	2017	China	Prospective cohort	42.93	MAP 10 (8.8), MSAP 12 (10.6), SAP 91 (80.6)	OGTT (FBG, 2hPG), FINS, HBA1c, HOMA-β, HOMA-IR	113	Not stated	IGT 33 (29.2)	34 (30.1)	Not stated	Not stated	Not stated
Nikkola (27)	2017	Finland	Prospective cohort	126	MAP 35 (74.5), MSA and SAP, 12 (25.5)	HbA1c, OGTT, FPG, glucagon C-peptide test	47	14 (29.8)	13 (27.7)	13 (27.7)	Not stated	Not stated	Not stated
Winter Gasparoto (28)	2015	Brazil	Prospective cohort	34.8	All SAP	OGTT, C-peptide, HOMA	14	Not stated	7 (58.3)	5 (41.7)	Not stated	Not stated	Not stated
Vujasinovic (29)	2014	Slovenia	Prospective cohort	32.4	MAP 67 (67.0), MSAP 15 (15.0), SAP 18 (18.0)	HbA1c, OGTT	75	Not stated	Not stated	6 (8.0) (from author)	Not stated	Not stated	Not stated
Nikkola (30)	2013	Finland	Prospective cohort	61.8	Not stated	FBG, HbA1c, OGTT, C-peptide	15	0 (0)	1 (6.7)	0 (0)	Not stated	Not stated	Not stated
Wu (31)	2011	China	Prospective cohort	42	MAP 24 (40.7), SAP 35 (59.7)	FBG, HbA1c, FBI, C-peptide, HOMA	59	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated
Uomo (32)	2010	Italy	Prospective cohort	179.5 (median)	All SAP	FBG, OGTT	38	Not stated	Not stated	6 (15.9)	Not stated	Not stated	Not stated
Pelli (33)	2009	Finland	Prospective cohort	47 (median)	MAP 41 (75), SAP 13 (25)	FBG, HbA1c, OGTT	46	one time 10 (19), two times 1 (18.5), three times 1 (18.5), (baseline 54)	IFG 7 (15.2), IGT 5 (10.9)	5 (10.9)	Not stated	Not stated	Not stated
Boreham (16)	2003	UK	Prospective cohort	3	MAP 16 (69.6), SAP 7 (30.4)	FPG	23	No, only a single attack	Not stated	4 (17.4)	Not stated	1 (4.3)	Not stated
Ibars (34)	2002	Spain	Prospective cohort	1, 6 and 12	MAP 45 (71.0), SAP 18 (28.0)	OGTT, arginine test	55	Not stated	7 (12.7)	6 (10.9)	Not stated	Not stated	Not stated
Doepel (35)	1993	Finland	Prospective cohort	74.4	All SAP	BG, C-peptide, HbA1, HbA1c, OGGT	24	Not stated	IGT 4 (16.7)	7 (29.2)	4 (16.7)	1 (4.2)	2 (8.3)

Table 3. The Methodological Quality of Studies Stratified by Study Design[a]

Study	Year	Measured Items on the Newcastle-Ottawa Scale			Scores (High/Low Quality)
		Patient Selection	Comparability	Exposure/Outcome	
Cohort		(1) Representativeness of the exposed cohort, (2)Selection of non-exposed cohort, (3)Ascertainment of exposure, (4)Demonstration that the outcome of interest was not present at the start of the study	(1) Comparability of cohorts on the basis of the design or analysis (maximum two points)	(1) Assessment of outcome, (2) Follow-up was long enough for outcomes to occur, (3) Adequacy of follow-up of cohorts	low quality: 0-4, high quality: 5 - 9
Tu (25)	2018	(1)[a] Truly representative of patients with AP, (2)[a] Endocrine assessment was done for patients selected from exposed cohort, (3)[a] Prospective recruitment of patients who met the criteria for AP, (4)[a] Outcome of interest was not present at the start of study	(1)[a] Study controls for severity of AP	(1)[a] Outcome was assessed by independent endocrine testing, (2)[a] Follow-up was long enough for outcome to occur, (3)[a] All subjects were accounted for	8
Tu (26)	2017	(1)[a] Truly representative of patients with AP, (2)[a] Endocrine assessment was done for patients selected from exposed cohort, (3)[a] Prospective recruitment of patients who met the criteria for AP, (4)[a] Outcome of interest was not present at the start of study	(1)[a] Study controls for severity of AP	(1)[a] Outcome was assessed by independent endocrine testing, (2)[a] Follow-up was long enough for outcome to occur, (3)[a] All subjects were accounted for	8
Nikola (27)	2017	(1)[a] Truly representative of patients with AP, (2)[a] Endocrine assessment was done for patients selected from exposed cohort, (3)[a] Prospective recruitment of patients who met the criteria for AP	(1)[a] Study controls for severity of AP and etiology	(1)[a] Outcome was assessed by independent endocrine testing, (2)[a] Follow-up was long enough for outcome to occur, (3)[a] All subjects were accounted for	7
Winter Gasparoto (28)	2015	(1)[a] Truly representative of patients with AP, (2)[a] Endocrine assessment was done for patients selected from exposed cohort (3)[a] Prospective recruitment of patients who met the criteria for AP	(1)[a] Study controls for severity of AP	(1)[a] Outcome was assessed by independent endocrine testing, (2)[a] Follow-up was long enough for outcome to occur, (3)[a] All subjects were accounted for	7
Vujasinovic (29)	2014	(1)[a] Truly representative of patients with AP, (2)[a] Endocrine assessment was done for patients selected from exposed cohort, (3)[a] Prospective recruitment of patients who met the criteria for AP, (4)[a] Outcome of interest was not present at the start of study	(1)[a] Study controls for severity of AP	(1)[a] Outcome was assessed by independent endocrine testing, (2)[a] Follow-up was long enough for outcome to occur, (3)[a] All subjects were accounted for	8
Nikola (30)	2013	(1)[a] Truly representative of patients with AP, (2)[a] Endocrine assessment was done for patients selected from exposed cohort, (3)[a] Prospective recruitment of patients who met the criteria for AP, (4)[a] Outcome of interest was not present at the start of study	(1)[a] Study controls for severity of AP and etiology	(1)[a] Outcome was assessed by independent endocrine testing, (2)[a] Follow-up was long enough for outcome to occur, (3)[a] All subjects were accounted for	8
Wu (31)	2011	(1)[a] Truly representative of patients with AP, (2)[a] Endocrine assessment was done for patients selected from exposed cohort, (3)[a] Prospective recruitment of patients who met the criteria for AP, (4)[a] Outcome of interest was not present at the start of study	(1)[a] Study controls for severity of AP	(1)[a] Outcome was assessed by independent endocrine testing, (2)[a] Follow-up was long enough for outcome to occur, (3)[a] All subjects were accounted for,	8

Uomo (32)	2010	(1)[a] Truly representative of patients with AP, (2)[a] Endocrine assessment was done for patients selected from exposed cohort, (3)[a] Prospective recruitment of patients who met the criteria for AP	(1)[a] Study controls for severity of AP	(1)[a] Outcome was assessed by independent endocrine testing, (2)[a] Follow-up was long enough for outcome to occur, (3)[a] Subjects lost to follow up unlikely to introduce bias - description provided on those who lost	7
Pelli (33)	2009	(1)[a] Truly representative of patients with AP, (2)[a] Endocrine assessment was done for patients selected from exposed cohort, (3)[a] Prospective recruitment of patients who met the criteria for AP	(1)[a] Study controls for severity of AP and etiology	(1)[a] Outcome was assessed by independent endocrine testing, (2)[a] Follow-up was long enough for outcome to occur, (3)[a] All subjects were accounted for	7
Boreham (16)	2003	(1)[a] Truly representative of patients with AP, (2)[a] Endocrine assessment was done for patients selected from exposed cohort, (3)[a] Prospective recruitment of patients who met the criteria for AP, (4)[a] Outcome of interest was not present at the start of study	(1)[a] Study controls for severity of AP	(1)[a] Outcome was assessed by independent endocrine testing, (2)[a] Follow-up was long enough for outcome to occur, (3)[a] All subjects were accounted for	8
Ibars (34)	2002	(1)[a] Truly representative of patients with AP, (2)[a] Endocrine assessment was done for patients selected from exposed cohort, (3)[a] Ascertainment of exposure (diagnosis of AP) was through secure surgical records	(1)[a] Study controls for severity of AP and etiology	(1)[a] Outcome was assessed by independent endocrine testing, (2)[a] Follow-up was long enough for outcome to occur, (3)[a] Subjects lost to follow up unlikely to introduce bias - description provided on those who lost	7
Doepel (35)	1993	(1)[a] Truly representative of patients with AP, (2)[a] Endocrine assessment was done for patients selected from exposed cohort, (3)[a] Prospective recruitment of patients who met the criteria for AP	(1)[a] Study controls for severity of AP	(1)[a] Outcome assessed by independent endocrine testing, (2)[a] Follow-up was long enough for outcome to occur, (3)[a] Subjects lost to follow up unlikely to introduce bias - description provided on those who lost	7

Abbreviation: AP, acute pancreatitis.
[a]Points on the scale.

Table 4. Subgroup Analysis According to the Follow-up Time

Follow-up Time, mo	Prediabetes and/or DM						Prediabetes						DM					
	No. of Studies	Total No. of Patients	No. of Patients with Prediabetes and/or DM	Pooled Prevalence, (95% CI)	I^2, (%)	Relative Risk, (95% CI)[a]	No. of Studies	No. of Studies	No. of Patients with Prediabetes	Pooled Prevalence, (95% CI)	I^2, (%)	Relative Risk, (95% CI)[a]	No. of Studies	Total No. of Patients	No. of Patients with DM	Pooled Prevalence, (95% CI)	I^2, (%)	Relative risk (95% CI)[a]
≤ 12	1 (34)	56	13	0.23 [0.14; 0.37]	b	Not applicable	1 (34)	56	7	0.13 [0.06; 0.25]	b	Not applicable	2 (16, 34)	79	10	0.13 [0.07; 0.23]	0	1.03 [0.51; 2.09]
12 - 36	1 (28)	14	12	0.86 [0.69; 1.00]	b	3.69 [1.69; 6.22]	1 (28)	14	7	0.50 [0.30; 0.84]	b	4.00 [1.68; 9.53]	2 (28, 29)	89	11	0.17 [0.04; 0.74]	87	1.35 [0.30; 6.11]
36 - 60	3 (25, 26, 33)	415	238	0.55 [0.47; 0.66]	60	2.28 [1.69; 3.09]	3 (25, 26, 33)	415	117	0.28 [0.24; 0.33]	0	2.24 [1.44; 3.50]	3 (25, 26, 33)	415	121	0.27 [0.19; 0.38]	68	2.12 [1.42; 3.16]
> 60	3 (27, 30, 35)	86	38	0.45 [0.28; 0.73]	67	1.74 [0.86; 3.55]	3 (27, 30, 35)	86	18	0.21 [0.12; 0.37]	27	1.57 [0.84; 2.93]	4 (27, 30, 32, 35)	124	26	0.23 [0.15; 0.35]	26	1.63 [1.02; 2.59]

Abbreviation: DM, diabetes mellitus.
[a] Compared to follow-up ≤ 12 months after the first attack of AP.
[b] Not enough number of studies.