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ARTICLE

Exocrine Pancreatic Dysfunction Increases the Risk of New-Onset Diabetes Mellitus: Results of a Nationwide Cohort Study

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It is well established that individuals with diabetes mellitus (DM) may develop exocrine pancreatic dysfunction (EPD) requiring pancreatic enzyme replacement therapy, whereas the converse relationship has been poorly studied. Pancreatitis is a disease that is well suited to investigate the latter as it is often characterized by the development of EPD and/or new-onset DM. The aim was to investigate the association between EPD and the risk of new-onset DM in individuals after the first attack of pancreatitis. Using nationwide pharmaceutical dispensing data and hospital discharge data, this cohort study included a total of 9,124 post-pancreatitis individuals. EPD was defined as having two or more dispensing records of pancreatic enzymes. Considering EPD as a time-dependent variable, multivariable Cox regression analysis was conducted. A 1-year lag period between EPD and DM was introduced to minimize reverse causality. Age, sex, ethnicity, alcohol consumption, tobacco smoking, social deprivation index, Charlson comorbidity index, and use of proton pump inhibitors were adjusted for. In the overall cohort, EPD was associated with a significantly higher risk for new-onset DM (adjusted hazard ratio, 3.83; 95% confidence interval, 2.37–6.18). The association remained statistically significant when a 1-year lag period was applied (adjusted hazard ratio, 2.51; 95% confidence interval, 1.38–4.58), as well as when the analysis was constrained to mild acute pancreatitis (4.65; 2.18–9.93). The findings suggest that individuals with EPD, even those without extensive mechanistic destruction of the pancreas, are at an increased risk for new-onset DM. Purposely designed studies are warranted to investigate mechanisms behind the association and if the mechanisms could be targeted therapeutically.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
☑ Individuals with diabetes mellitus (DM) have high frequency of exocrine pancreatic dysfunction (EPD) requiring pancreatic enzyme replacement therapy. No study has investigated the association between EPD and new-onset DM. Individuals with pancreatitis frequently develop EPD and/or DM during follow-up and this offers an opportunity to investigate the temporal relationship between the two disorders.

WHAT QUESTION DID THIS STUDY ADDRESS?
☑ Is EPD associated with the risk of new-onset DM in post-pancreatitis individuals, including those after mild acute pancreatitis?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?
☑ Individuals with EPD after first attack of pancreatitis are at an increased risk of new-onset DM. This holds true in individuals after mild acute pancreatitis.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?
☑ EPD may need to be considered as a risk factor for new-onset DM. The mechanism is likely to be multifaceted and is not constrained to mechanical destruction of β-cells in the pancreas.

The burden of diabetes mellitus (DM) is colossal. Globally, DM resulted in estimated 1.6 million deaths[1] and 57 million years of healthy life lost in 2016.[2] It is also increasingly recognized that there are multiple underlying causes of DM. In particular, DM develops secondary to pancreatitis in up to 83% of individuals.[3,4] This type of DM (recently termed "post-pancreatitis DM") leads to 14.8 excess deaths per 1,000 person-years and up to 40% increased risk of hospitalization, as compared with type 2 DM.[5] Further, if not medicated, post-pancreatitis DM results in 68 excess deaths per 1,000 person-years compared with type 2 DM.[6]

Exocrine pancreatic dysfunction (EPD) may develop secondary to dozens of diseases and conditions (e.g., cystic fibrosis, pancreatic cancer, several genetic disorders, and after pancreatic/gastrointestinal surgery). However, the most common cause of EPD is pancreatitis. It is known that a substantial number of individuals following pancreatitis develop EPD (including those after mild acute pancreatitis

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and early chronic pancreatitis).[7,8] EPD leads to several dysfunctions, including but not limited to fat malabsorption and deficiency of fat-soluble vitamins (i.e., vitamins A, D, E, and K). The classical consequences of the latter are night blindness, osteoporosis and fractures, neuropathy, hemolytic anemia, and coagulopathy.[9,10] A meta-analysis of 21 prospective studies demonstrated that deficiency of fat-soluble vitamins is associated with an increased risk of new-onset DM.[11] Individuals with EPD often require pancreatic enzyme replacement therapy. Although the indications for pancreatic enzyme replacement therapy may vary, the therapy ameliorates EPD and improves the associated gastrointestinal symptoms, as a meta-analysis of 14 randomized controlled trials showed.[12]

Despite compelling evidence from *in vivo* and *in vitro* studies on the intimate morphological and functional relationship between pancreatic acini and the islets of Langerhans (epitomized in the "insulo-acinar axis" notion),[13–15] the relationship between exocrine dysfunction and endocrine dysfunction of the pancreas remains poorly characterized in humans. To date, clinical investigations on the temporal relationship between exocrine dysfunction and endocrine dysfunction of the pancreas have been disproportionately skewed toward studying DM as a risk factor for EPD. A systematic review identified a total of 26 studies that used direct or indirect pancreatic function tests in people with DM.[16] Two other systematic reviews identified a total of 55 studies that investigated pancreas volume and size (derived from modern radiological modalities) as a proxy for secretory reserve of pancreatic acinar cells in people with DM.[17,18] By contrast, evidence on the converse relationship (i.e., EPD as a risk factor for new-onset DM) has been only circumstantial. Part of the reason for the lack of studies is a difficulty to find the optimal study population, as there are many underlying causes for EPD and most of them do not subsequently result in high frequency of new-onset DM. Individuals after pancreatitis, the most common disease of the exocrine pancreas[19] that frequently results in both new-onset EPD and new-onset DM,[20] represent a suitable relatively homogeneous study population to explore the relationship between EPD and new-onset DM. Indirect evidence comes from several recent systematic reviews in the setting of pancreatitis that have consistently shown that the frequency of EPD typically does not increase over time after an attack of pancreatitis,[7,8,21] whereas that of new-onset DM increases.[22] However, there have been no purposely designed studies to investigate the association between EPD and DM. Moreover, large-scale investigations on EPD are scarce as measuring exocrine pancreatic function (through duodenal intubation, hormone injection, consumption of high-fat diets, or fecal fat analysis) is infeasible in large populations. That is why previous large-scale studies used pancreatic enzyme replacement therapy as a proxy for EPD.[9,23,24] Given that individuals with EPD often have deficiency of fat-soluble vitamins[25,26] and taking into account evidence on the relationship between deficiency of fat-soluble vitamins and new-onset DM,[11] we hypothesized that EPD increases the risk for new-onset DM.

The primary aim was to investigate the association between EPD and new-onset DM in individuals after the first attack of pancreatitis, considering EPD as a time-varying risk factor. The secondary aim was to examine the impact of fat-soluble vitamin supplementation on the frequency of new-onset DM in individuals with and without EPD.

METHODS

Data source

All data were provided in a de-identified form by the Ministry of Health Analytical Services (National Health Board, New Zealand). Nationwide hospital admission and mortality databases (January 1, 1998, to December 31, 2015) were linked to nationwide pharmaceutical dispensing database (January 1, 2006, to December 31, 2015). The hospitalization data included information on demographics (age, sex, and ethnicity) and hospitalization (tenth revision of the International Classification of Diseases (ICD-10) codes, date of admission, ICD-10 codes for procedures, and date of procedures). The pharmaceutical data covered primary to tertiary health care and contained information on chemical name and dispensed date. The nationwide hospital admission and pharmaceutical dispensing databases individually have a positive predictive value of 88% in identifying individuals with DM.[27] Ethics approval was waived in accordance with the Ministry of Health guidelines.

Study cohort

Using the above nationwide databases, we identified adults (≥ 20 years-old) who were first admitted for acute pancreatitis (ICD-10, K85.0–K85.9 in the primary position) or chronic pancreatitis (K86.0; K86.1 in any position) from January 1, 2007 to December 31, 2015. When an individual had both diagnoses during the study period, chronic pancreatitis was prioritized. The absence of pancreatitis prior to 2007 was confirmed by tracking nationwide hospital admission data back to 1998. Date of first admission for acute pancreatitis or chronic pancreatitis was set as index date. The following exclusion criteria were applied: diagnostic codes of any cancer (ICD-10, Cxx), type 1 DM (E10), cystic fibrosis (E84), celiac disease (K90.0), Zollinger-Ellison syndrome (E16.4), Shwachman-Diamond syndrome (D61.0), Pearson marrow-pancreas syndrome (D64.0), and Johanson-Blizzard syndrome (Q87.8) in any position between 1998 and 2015; pancreas-related intervention (e.g., pancreatectomy) prior to the index date; and bariatric surgery (ICD-10, Z98.84; 3051100; 3051101; 3051200) prior to the index date. Individuals with diagnostic codes of type 2 DM (ICD-10, E11) or other specified DM (E13) in any position and/or at least one dispensing record of oral hypoglycemic agents prior to or within 90 days after the index date were also excluded.

Identification of exocrine pancreatic dysfunction and diabetes mellitus

The exposure variable was newly developed EPD after the index date, defined as having at least two dispensing records of pancreatic enzymes: the first record more than 90 days after index date; and the second record within a 6-month period after the first record. Of these, individuals who had a dispensing record of pancreatic enzyme at least 1 year prior to or within 90 days after index date were

classified as unexposed. Date of the second dispensing record of pancreatic enzyme was considered as the date of EPD.

The end point was new-onset DM, defined as having diagnostic codes of type 2 DM (ICD-10, E11) or other specified DM (E13) in any position and/or having at least one dispensing record of oral hypoglycemic agents more than 90 days after the index date (whichever came first). All individuals were confirmed not to have diagnostic codes of type 1 DM (ICD-10, E10) between 1998 and 2015; and diagnostic codes of type 2 DM (ICD-10, E11) or other specified DM (E13) in any position prior to or within 90 days after the index date. They also had no dispensing record of oral hypoglycemic agents prior to or within 90 days after the index date. Study individuals were followed up from the index date to the date of the end point, the end of the study period (December 31, 2015), or date of death (whichever occurred first).

Definitions of variables

Alcohol consumption was defined as the presence of diagnostic codes relevant to alcohol-related disorders or problems in the 5 years prior to the index date.[28] Smoking was identified using relevant diagnostic codes (ICD-10, Z720; Z8643; and Z87.891) during the entire observation period. Ethnicity was classified as European, Māori or Pacific Islander, Asian, and others. Social deprivation index for each area of residence in New Zealand (ranging from 1 to 10) was given to each individual; and this variable was categorized into quartiles, with an additional category for missing values.[29] Charlson comorbidity index was calculated based on a wide spectrum of comorbidities (e.g., cardiovascular disease, pulmonary disease, renal disease, liver disease, dementia, and cancer) during the previous 5 years before the index date, in line with the previous literature.[30] Given that concurrent use of proton pump inhibitors and pancreatic enzymes is common (with a view to preventing the deactivation of pancreatic enzymes by gastric acid) and taking into account that there is some evidence that proton pump inhibitors may improve glycemic control,[31,32] individuals with at least one dispensing record of omeprazole, lansoprazole, and pantoprazole (the only subsidized drugs of this class in New Zealand) on or after the index date were deemed as users of proton pump inhibitors.

Recurrent acute pancreatitis was defined as having two or more episodes of acute pancreatitis as a primary diagnosis. Readmission within 30 days after discharge date of first admission for acute pancreatitis was not regarded as a new episode of acute pancreatitis.[33] Alcohol-related etiology of pancreatitis was determined using the above definition of alcohol consumption. Severe acute pancreatitis was defined as having diagnostic codes relevant to organ failure and/or infection within a 3-month period from the index date[34]; otherwise, individuals were classified as having mild acute pancreatitis. Advanced chronic pancreatitis was defined as having pancreas-related intervention after the index date[35]; otherwise, individuals were categorized as having early chronic pancreatitis.

Fat-soluble vitamin supplementation was defined as at least one dispensing record of vitamin A (beta-carotene), vitamin D (cholecalciferol; calcitriol; alphacalcidol), vitamin E (alpha tocopherol acetate), or vitamin K (menadione sodium bisulfite; phytomenadione) between the index date and the date of censoring.

Statistical analysis

All analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC). *T*-tests (for age) and χ^2 tests (for the other variables) were used to examine differences in the characteristics between individuals with and without new-onset DM. The mean (SE) follow-up period was calculated using the Kaplan–Meier method. Crude and multivariable time-dependent Cox regression analyses were conducted to estimate the risk of DM related to EPD in the overall cohort, individuals with acute pancreatitis only, and individuals with chronic pancreatitis only (primary aim). In these analyses, EPD was entered as a time-dependent variable (**Figure 1**). Individuals were classified as those without EPD during the time between the index date and development of EPD (i.e., immortal time), from which point they were then reclassified as those with EPD until the date of censoring. This approach was used to address immortal time bias due to varied time of EPD development.[36] The multivariable model included age, sex, ethnicity, social deprivation index, alcohol consumption, tobacco smoking, Charlson comorbidity index, and use of proton pump inhibitors as covariates. In all Cox regression models, the reference group was individuals without EPD. In addition, to examine the effect of fat-soluble vitamin supplementation on the risk of DM related to EPD (secondary aim), the same Cox regression analyses were repeated in individuals with vs. without fat-soluble vitamin supplementation. Significance of the difference in the risk of new-onset DM associated with EPD between individuals with and without fat-soluble vitamin supplementation was tested using the method described by Altman and Bland.[37] The risk of new-onset DM associated with EPD was expressed as hazard ratios (HRs) with 95% confidence intervals (CIs).

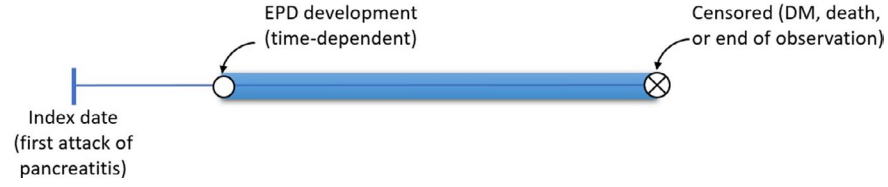

Figure 1 Scheme of the principal analysis. EPD was considered as a time-dependent variable in Cox regression models. Individuals were classified as having no EPD between index date and time of development of EPD, from which point they were then reclassified as those with EPD until the end of follow-up. EPD, exocrine pancreatic dysfunction; DM, diabetes mellitus.

Four prespecified subgroup analyses were conducted to investigate the impact of characteristics of pancreatitis (etiology, recurrence of acute pancreatitis, severity of acute pancreatitis, and advancement of chronic pancreatitis) on the association between EPD and DM. In the overall cohort, the same Cox regression analysis as the main analysis was conducted after stratification by etiology (alcohol-related pancreatitis vs. non-alcohol-related pancreatitis). In this analysis, alcohol consumption was excluded from the list of covariates above. In individuals with acute pancreatitis only, two subgroup analyses were conducted after stratification by recurrence (recurrent acute pancreatitis vs. single episode of acute pancreatitis) and severity of acute pancreatitis (severe acute pancreatitis vs. mild acute pancreatitis). In individuals with chronic pancreatitis only, the same Cox regression analysis as the main analysis was conducted in advanced chronic pancreatitis vs. early chronic pancreatitis. A prespecified sensitivity analysis was also performed. The association between EPD and DM was investigated using 1-year lag period between EPD and DM. This analysis was conducted to minimize the possibility of reverse causality by excluding individuals who developed DM within 1 year after EPD.

RESULTS

Characteristics of the cohort

A total of 9,124 individuals with pancreatitis (8,206 with acute pancreatitis and 918 with chronic pancreatitis) were observed for a mean period of 7.57 (SE, 0.02) years. The mean ± SD age of the study individuals was 55.5 ± 19.4 years and men accounted for 48.4% of the cohort. The proportions of men ($P < 0.001$), tobacco ever-smokers ($P < 0.001$), and users of proton pump inhibitors ($P = 0.012$) were significantly higher in individuals with DM. Other characteristics are presented in **Table 1**.

Association between exocrine pancreatic dysfunction and new-onset diabetes mellitus

The cumulative incidence of DM was higher in individuals with EPD ($n = 23$, 17.0%) than in those without EPD ($n = 470$, 5.2%, $P < 0.001$; **Figure 2**). The median (interquartile range) time between EPD and DM was 661 (206–1,408) days. In the overall cohort, individuals with EPD had a significantly higher risk for DM (adjusted HR, 3.83; 95% CI, 2.37–6.18; **Table 2**). In the sensitivity analysis, constrained to individuals with > 1 year between EPD and DM ($n = 7,300$), EPD

Table 1 Characteristics of the study cohort

		Exposure status			Outcome status		
	Total ($n = 9,124$)	Individuals without EPD ($n = 8,989$)	Individuals with EPD ($n = 135$)	*P* value	Individuals without DM ($n = 8,631$)	Individuals with DM ($n = 493$)	*P* value
Age, years, mean (SD)	55.5 (19.4)	55.5 (19.4)	55.5 (16.6)	0.29	55.5 (19.5)	55.3 (17.5)	0.77
Men, *n* (%)	4,414 (48.4)	4,325 (48.1)	89 (65.9)	< 0.001	4,128 (47.8)	286 (58.0)	< 0.001
Ethnicity, *n* (%)				0.002			< 0.001
European	6,647 (72.9)	6,529 (72.6)	118 (87.4)		6,348 (73.6)	299 (60.7)	
Māori or Pacific Islander	1,744 (19.1)	1,733 (19.3)	11 (8.2)		1,595 (18.5)	149 (30.2)	
Asian	448 (4.9)	445 (5.0)	3 (2.2)		420 (4.9)	28 (5.7)	
Others	285 (3.1)	282 (3.1)	3 (2.2)		268 (3.1)	17 (3.5)	
Social deprivation index, *n* (%)				0.10			0.003
Quartile 1	2,452 (26.9)	2,403 (26.7)	49 (36.3)		2,338 (27.1)	114 (23.1)	
Quartile 2	1,615 (17.7)	1,591 (17.7)	24 (17.8)		1,545 (17.9)	70 (14.2)	
Quartile 3	2,116 (23.2)	2,089 (23.2)	27 (20.0)		2,001 (23.2)	115 (23.3)	
Quartile 4	2,385 (26.1)	2,359 (26.2)	26 (19.3)		2,214 (25.7)	171 (34.7)	
Missing	556 (6.1)	547 (6.1)	9 (6.7)		533 (6.2)	23 (4.7)	
Alcohol consumption, *n* (%)	1,041 (11.4)	1,009 (11.2)	32 (23.7)	< 0.001	981 (11.4)	60 (12.2)	0.64
Smoking, *n* (%)	4,320 (47.4)	4,240 (47.2)	80 (59.3)	0.007	4,029 (46.7)	291 (59.0)	< 0.001
Charlson comorbidity index				0.022			0.078
0	8,285 (90.8)	8,167 (90.9)	118 (87.4)		7,850 (91.0)	435 (88.2)	
1	528 (5.8)	516 (5.7)	12 (8.9)		487 (5.6)	41 (8.3)	
2	176 (1.9)	176 (2.0)	0 (0.0)		168 (1.9)	8 (1.6)	
3+	135 (1.5)	130 (1.5)	5 (3.7)		126 (1.5)	9 (1.8)	
Use of proton pump inhibitors	4,966 (54.4)	4,846 (53.9)	120 (88.9)	< 0.001	4,670 (54.1)	296 (60.0)	0.012

P values were from *t*-tests (for age) and χ^2 tests (for categorical variables) between individuals with and without either EPD or DM.
EPD, exocrine pancreatic dysfunction; DM, diabetes mellitus.

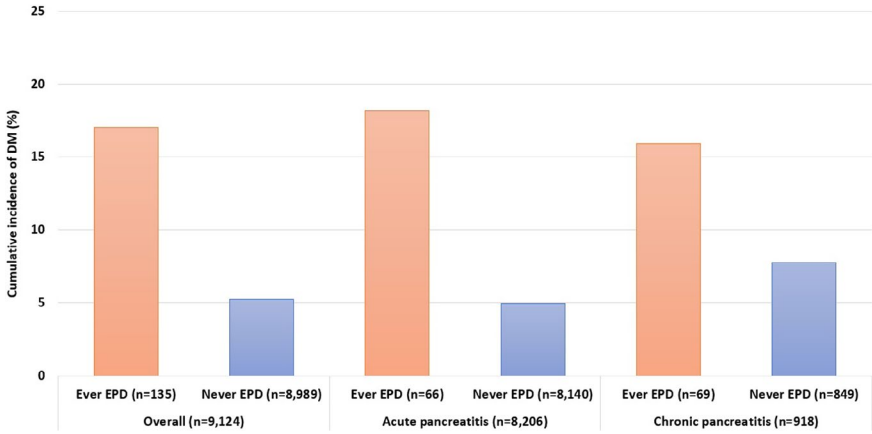

Figure 2 Cumulative incidence of new-onset diabetes mellitus, stratified by the exocrine pancreatic dysfunction status. DM, diabetes mellitus; EPD, exocrine pancreatic dysfunction.

was also associated with a significantly higher risk for DM (adjusted HR, 2.51; 95% CI, 1.38–4.58).

Effect of characteristics of pancreatitis

In the analysis stratified by etiology, individuals with EPD following both alcohol-related pancreatitis (adjusted HR, 3.89; 95% CI, 1.34–11.28) and non-alcohol-related pancreatitis (adjusted HR, 3.97; 95% CI, 2.32–6.82) had significantly higher risks for DM (**Figure 3**). Among acute pancreatitis individuals only, EPD was associated with a significantly higher risk of DM (adjusted HR, 4.85; 95% CI, 2.57–9.16; **Table 2**). In the analysis stratified by severity of acute pancreatitis, the higher risk for DM associated with EPD was statistically significant both in individuals with mild acute pancreatitis (adjusted HR, 4.65; 95% CI, 2.18–9.93) and in those with severe acute pancreatitis (adjusted HR, 7.12; 95% CI, 2.08–24.32; **Figure 3**). In the analysis stratified by recurrence, the risks for DM associated with EPD were similarly high in individuals with single episode of acute pancreatitis and recurrent acute pancreatitis (**Figure 3**). Among individuals with chronic pancreatitis only, EPD was associated with a significantly higher risk for DM (adjusted HR, 3.14; 95% CI, 1.44–6.84; **Table 2**). The higher risk for DM associated with EPD was statistically significant in individuals with advanced chronic pancreatitis (adjusted HR, 3.83; 95% CI, 1.15–12.79) and just missed the conventional threshold of statistical significance in individuals with early chronic pancreatitis (adjusted HR, 2.72; 95% CI, 0.90–8.17; **Figure 3**).

Effect of fat-soluble vitamin supplementation

In the overall cohort, 7,634 (83.7%) individuals did not receive fat-soluble vitamin supplementation, whereas 1,490 (16.3%) did. In individuals who did not receive fat-soluble vitamin supplementation, the proportion of new-onset DM was 5.5% (n = 414) in those without EPD, whereas it was 19.4% (n = 21) in those with EPD. The risk of new-onset DM was statistically significant in individuals who did not receive fat-soluble vitamin supplementation, in both crude (HR, 4.21; 95% CI, 2.59–6.84) and adjusted (HR, 4.34; 95% CI, 2.65–7.13) analyses. In individuals who received fat-soluble vitamin supplementation, the proportion of new-onset DM was 3.8% (n = 56) in those without EPD, whereas it was 7.4% (n = 2) in those with EPD (P = 0.28). The risk of new-onset DM was not statistically significant in individuals who received fat-soluble vitamin supplementation, in both crude

Table 2 Associations between exocrine pancreatic dysfunction and new-onset diabetes mellitus

	No. of events/EPD group	Mean (SE) follow up years	Crude HR (95% CI)	Adjusted HR (95% CI)
Overall				
Never EPD	470/8,989	7.59 (0.02)	1.00	1.00
Ever EPD	23/135	6.81 (0.22)	3.66 (2.28–5.86)	3.83 (2.37–6.18)
Acute pancreatitis only				
Never EPD	404/8,140	7.61 (0.02)	1.00	1.00
Ever EPD	12/66	4.12 (0.14)	4.36 (2.33–8.18)	4.85 (2.57–9.16)
Chronic pancreatitis only				
Never EPD	66/849	7.27 (0.08)	1.00	1.00
Ever EPD	11/69	6.97 (0.30)	2.22 (1.06–4.65)	3.14 (1.44–6.84)

Adjusted hazard ratios were from time-dependent multivariable Cox regression models including age, sex, ethnicity, alcohol consumption, smoking, social deprivation index, Charlson comorbidity index, and use of proton pump inhibitors.
95% CI, 95% confidence interval; EPD, exocrine pancreatic dysfunction; HR, hazard ratio.

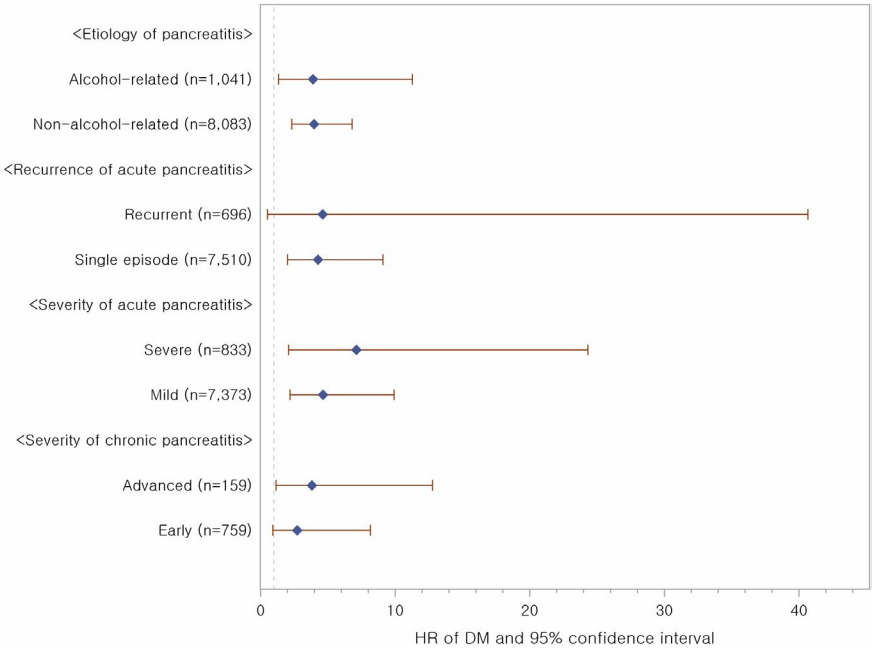

Figure 3 Hazard ratios of new-onset diabetes mellitus in the study subgroups. HR, hazard ratio; DM, diabetes mellitus; EPD, exocrine pancreatic dysfunction.

(HR, 1.40; 95% CI, 0.19–10.14) and adjusted analyses (HR, 1.54; 95% CI, 0.20–11.69). The difference in adjusted HRs between individuals with and without fat-soluble vitamin supplementation was not statistically significant (P = 0.41).

DISCUSSION

The present study is the first to investigate the association between EPD and new-onset DM in a large cohort, with EPD being a time-dependent variable. Focusing the study on individuals with first attack of pancreatitis enabled us to investigate the research question in a homogeneous study population that has high frequency of EPD and is at high risk for new-onset DM. The use of nationwide data from all the 20 District Health Boards in the country enabled us to minimize the possibility of selection bias. In addition, the comprehensive pharmaceutical dispensing data from primary to tertiary health care enabled robust adjustment for concomitant use of drugs (specifically, proton pump inhibitors, which are often administered in individuals with EPD and may affect glucose metabolism by means of increasing gastrin levels).[31,32] In the overall cohort, individuals with EPD had a 3.8-times significantly higher risk for new-onset DM. The association remained significant after adjusting for a range of covariates, including Charlson comorbidity index. The average duration between EPD and new-onset DM was 1.8 years and the introduction of 1-year lag period between EPD and DM (to minimize the possibility of reverse causality) did not have a material impact on the studied association. There was no substantial difference in the risk of new-onset DM associated with EPD between individuals with acute pancreatitis and those with chronic pancreatitis.

Considering possible mechanisms underlying the link between EPD and risk of new-onset DM, one could argue that the observed association is solely attributed to severity of pancreatitis (i.e., extensive pancreatic necrosis or fibrosis) and the resulting mechanical destruction of a large number of β cells in the pancreas. However, this mechanism cannot explain the development of DM in all (in fact, most) individuals in the present study, as the association between EPD and new-onset DM was also significant in the analysis constrained to individuals after mild acute pancreatitis (adjusted HR, 4.65; 95% CI, 2.18–9.93). Given that both individuals with mild acute pancreatitis and those with some other conditions that cause EPD (e.g., pancreatic cancer, several genetic disorders, and post-gastrointestinal surgery) do not typically have mechanical destruction of the pancreas, our findings have broad implications and warrant purposely designed studies on the complementary mechanisms linking pre-existing EPD and new-onset DM.

One possible mechanism relates to the deficiency of fat-soluble vitamins in individuals with EPD. In particular, it is known that vitamin D deficiency is present in up to 94% of individuals with EPD,[25,26] and lower serum 25-hydroxyvitamin D concentration is associated with a higher risk for new-onset DM.[11] A large 2019 cohort study specified that, of all vitamin D metabolites, only plasma non-epimeric 25-hydroxyvitamin D3 stereoisomer (the largest component of total 25-hydroxyvitamin D) is inversely associated with incident DM.[38] Further, there is also ample evidence suggesting that supplementation of fat-soluble vitamins (in particular, vitamin D) may be beneficial in preventing DM. Specifically, a 2017 meta-analysis including 24 randomized trials concluded that vitamin D supplementation may significantly reduce blood glucose level and insulin resistance in individuals with DM.[39] Although a large 2019 randomized trial in individuals with prediabetes demonstrated that vitamin D3 supplementation at

a dose of 4,000 IU per day did not significantly decrease the risk of new-onset DM in individuals with prediabetes after a median follow-up of 2.5 years,[40] it is worth noting that 42.2% of the study individuals had normal serum 25-hydroxyvitamin D levels (≥ 30 ng/mL) before vitamin D supplementation and EPD status of the study individuals was unknown (although it is reasonable to presume that most of the study individuals had normal exocrine pancreatic function). This is different from individuals with EPD, the overwhelming majority of whom have vitamin D deficiency (up to 94.2% when defined as serum 25-hydroxyvitamin *D* < 30 ng/mL),[25,26] which can be normalized by oral vitamin D supplementation.[25] The present study showed that the association between EPD and new-onset DM was not significant in individuals who received fat-soluble vitamin supplementation (predominantly vitamin D), which suggests that deficiency of fat-soluble vitamins might be a pathophysiological mechanism behind the higher risk of new-onset DM associated with EPD. There is probably not enough granularity to suggest that fat-soluble vitamin supplementation reduces the risk of new-onset DM associated with EPD, due to the observational (and healthcare utilization-based) nature of the present study coupled with the possibility of insufficient study power to detect the effect of fat-soluble vitamin supplementation. Purposely designed clinical studies are now warranted to investigate whether deficiency of fat-soluble vitamins and its improvement affect blood glucose homeostasis specifically in individuals with EPD.

The other possible mechanism that underlies the association between EPD and new-onset DM relates to the mediating role of altered gut microbiota. Altered gut microbiota involves gut microbiota dysbiosis (disrupted microbial composition presented as decreased diversity)[41] as well as gut microbiota overgrowth (abnormally high number). Altered gut microbiota is known to induce metabolic disorders by promoting gut inflammation (e.g., increasing lipopolysaccharide endotoxins crossing the gut barrier).[41] In particular, there is growing evidence on altered gut microbiota as a predisposing factor for insulin resistance and type 2 DM via upregulating inflammatory state.[42,43] In addition, several studies have found altered microbiota in the small bowel (e.g., small bowel bacterial overgrowth) in individuals with EPD.[44–46] Specifically, individuals with EPD have a 2-times higher frequency of small bowel bacterial overgrowth compared with those without EPD.[44–46] Further, a 2019 population-based study demonstrated that exocrine pancreatic function (as measured by fecal pancreatic elastase) is independently associated with composition and diversity of gut microbiota.[47] The above findings may be attributed to a reduction in antibacterial compounds secreted by pancreatic acinar cells (e.g., cathelicidin-related antimicrobial peptides),[48] ileal braking due to malabsorption,[49] and disrupted integrity of intestinal interface (e.g., suppressed defensins in the ileum) due to vitamin D deficiency.[50] Taken together, it is plausible that altered gut microbiota in individuals with EPD may induce insulin resistance via promoting low-grade inflammation in the host, consequently leading to new-onset DM. Given that numerous gut microbiota-modulating interventions are being trialed (e.g., low FODMAP diet, fibers, Bifidobacterium and Lactobacillus species of probiotics, stimulation of production of small chain fatty acids)[41] and considering that it took (on average) nearly 2 years for DM to develop following EPD in the present study, it is likely that there will be a "window of opportunity" for preventing DM in individuals with EPD should the translational impact of interventions be confirmed in high-quality studies.

The present study proactively addressed several possible biases. First, although our aim was to investigate whether EPD affects the risk of developing DM, it is known that DM may affect the risk of developing EPD. To minimize the possibility of reverse causality, a prespecified sensitivity analysis with 1-year lag period between EPD and DM was conducted and the association between EPD and a higher risk of DM remained significant. Second, because timing of EPD varies during follow-up of individuals with pancreatitis, EPD was treated as a time-dependent variable in the Cox regression analysis. This minimized the possibility of immortal-time bias.[36] Third, previous population-based studies on EPD[9,23] used a rather liberal definition of EPD based on a single prescription of pancreatic enzymes only. The present study used the strictest criteria among published population-based studies, hence ensuring that the reported estimates are conservative. Last, given that a meta-analysis[8] showed a staggering 62% frequency of EPD during hospitalization in patients with pancreatitis and the frequency reduced to 35% during follow-up (which is in line with a 29% frequency in our meta-analysis[7] and a 27% frequency in the meta-analysis by Holleman *et al.*),[21] the present study purposely excluded individuals who had EPD not only prior to but also during the first attack of pancreatitis.

There are several limitations to be acknowledged. First, data on glycated hemoglobin were not available and, hence, not used for defining DM. This may have led to underestimation of the number of events. However, the underestimation is less likely to occur differentially between the exposed and unexposed groups, as the same identification method was used in both groups. Moreover, the used nationwide hospital admission and pharmaceutical dispensing databases are known to have high diagnostic performance in identifying individuals with DM.[27] Second, data on circulating levels of fat-soluble vitamins and micronutrients (e.g., zinc) were not available. Future studies measuring circulating levels of fat-soluble vitamins and micronutrients are warranted to understand better the mechanisms behind the association between EPD and DM. Third, there might have been unmeasured confounders, such as severity of EPD. It is likely that individuals with EPD in our cohort had moderate-to-severe EPD, as the identification was based on the use of pancreatic enzymes. The risk of new-onset DM is worth investigating also in individuals with mild EPD in future studies. Last, the identification of alcohol consumption, a known risk factor for EPD, was based on ICD codes. Although we used extensive diagnostic codes of alcohol-related disorders (in line with previously published studies),[28] the effect of heavy alcohol drinking (but having no alcohol-related disorders) on the studied association cannot be ruled out. Similarly, smoking status (another known risk factor for EPD) was defined based on ICD codes. However, we

attempted to minimize this limitation by identifying smokers during the entire study period (i.e., both before and after the index date).

In conclusion, the present study shows that individuals with EPD have a significantly increased risk of new-onset DM. This holds true specifically in a large fraction of individuals after mild acute pancreatitis (in whom the development of DM cannot be attributed to mechanical destruction of the islets of Langerhans). It appears that deficiency of fat-soluble vitamins might play a role in the mechanisms linking EPD and new-onset DM. Purposely designed studies are now warranted to unveil the complex pathophysiological mechanisms behind the association and to determine whether they can be targeted with a view to preventing new-onset DM that follows EPD.

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