Incidence, Demographics, and Clinical Characteristics of Diabetes of the Exocrine Pancreas (Type 3c): A Retrospective Cohort Study

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OBJECTIVE

This study was conducted to describe the incidence of diabetes following pancreatic disease, assess how these patients are classified by clinicians, and compare clinical characteristics with type 1 and type 2 diabetes.

RESEARCH DESIGN AND METHODS

Primary care records in England (n = 2,360,631) were searched for incident cases of adult-onset diabetes between 1 January 2005 and 31 March 2016. We examined demographics, diabetes classification, glycemic control, and insulin use in those with and without pancreatic disease (subcategorized into acute pancreatitis or chronic pancreatic disease) before diabetes diagnosis. Regression analysis was used to control for baseline potential risk factors for poor glycemic control (HbA$_{1c}$ ≥7% [53 mmol/mol]) and insulin requirement.

RESULTS

We identified 31,789 new diagnoses of adult-onset diabetes. Diabetes following pancreatic disease (2.59 [95% CI 2.38–2.81] per 100,000 person-years) was more common than type 1 diabetes (1.64 [1.47–1.82]; $P < 0.001$). The 559 cases of diabetes following pancreatic disease were mostly classified by clinicians as type 2 diabetes (87.8%) and uncommonly as diabetes of the exocrine pancreas (2.7%). Diabetes following pancreatic disease was diagnosed at a median age of 59 years and BMI of 29.2 kg/m^2. Diabetes following pancreatic disease was associated with poor glycemic control (adjusted odds ratio, 1.7 [1.3–2.2]; $P < 0.001$) compared with type 2 diabetes. Insulin use within 5 years was 4.1% (3.8–4.4) with type 2 diabetes, 20.9% (14.6–28.9) with diabetes following acute pancreatitis, and 45.8% (34.2–57.9) with diabetes following chronic pancreatic disease.

CONCLUSIONS

Diabetes of the exocrine pancreas is frequently labeled type 2 diabetes but has worse glycemic control and a markedly greater requirement for insulin.

Diabetes of the exocrine pancreas is thought to constitute 9% of diabetes in hospitalized patients (1). This form of diabetes results when a process, such as inflammation, neoplasia, or surgical resection, disrupts the global architecture or physiology of the pancreas, often resulting in both exocrine and endocrine dysfunction (2,3). Diabetes of the exocrine pancreas is now the suggested universal nomenclature (4); terms such as type 3c diabetes and secondary pancreatic diabetes have previously been used. To our

knowledge, preceding pancreatic disease has never been systematically identified in a cohort of people with diabetes in primary care, and thus, the comparative incidence and clinical characteristics of diabetes of the exocrine pancreas remain uncertain.

Recognizing the role of pancreatic damage in the development of a patient's diabetes is vital to inform appropriate management plans. In diabetes of the exocrine pancreas, the production of insulin is usually reduced. This is caused by β-cell dysfunction following pancreatic inflammation or by absolute β-cell loss (5,6). In addition, pancreatic polypeptide upregulates insulin receptor expression in the liver, and its loss can lead to hepatic insulin resistance (7), an important physiological difference between diabetes of the exocrine pancreas and type 1 diabetes. Glucagon production from pancreatic α-cells is also diminished, which may explain the episodes of severe hypoglycemia that are reported in some patients (8,9). Failure to recognize this altered physiology may result in suboptimal treatment. Newer incretin-based agents, such as glucagon-like peptide 1 receptor agonists ("incretins") and dipeptidyl peptidase 4 inhibitors ("gliptins"), would usually be considered contraindicated because of the presence of pancreatic damage (10). Insulinopenic patients with diabetes of the exocrine pancreas could be unfairly labeled as poorly compliant if they are misclassified as type 2 diabetes and show resistance to oral antihyperglycemic agents. Malabsorption secondary to pancreatic exocrine dysfunction is common, and pancreatic enzyme and vitamin D replacement is required to prevent malnutrition and osteoporotic bone disease (11–13).

Few studies have investigated how the distinct pathophysiology of diabetes of the exocrine pancreas manifests clinically. Limited evidence on the likelihood of significant hyperglycemia in diabetes of the exocrine pancreas makes deciding when to escalate antihyperglycemic therapy difficult. Retinopathy screening of patients with diabetes following chronic pancreatitis has suggested that when poor glycemic control is present in diabetes of the exocrine pancreas, the risk of microvascular disease is as high as with type 1 diabetes (14).

It has been suggested that 40% of hospital inpatients with diabetes of the exocrine pancreas are misdiagnosed as type 2 diabetes (1). Whether all diabetes that occurs following pancreatic disease should be considered diabetes of the exocrine pancreas is not clear, and there are currently no validated diagnostic criteria for diabetes of the exocrine pancreas. β-Cell failure does occur in adults with type 2 diabetes, but usually after a period of sustained insulin resistance (15), and only 1.7% of people with newly diagnosed type 2 diabetes required insulin as a first line therapy in a recent large U.K. retrospective cohort (16). If insulin is commonly required early in the course of diabetes in adults with prior pancreatic disease, it would imply that type 2 diabetes is not the usual explanation for diabetes in this patient group.

There is scarce evidence on how the clinical characteristics of diabetes following acute pancreatitis compare with those of diabetes following chronic pancreatic disease. Hypothetically, acute pancreatitis may have a lower propensity toward diabetes if an attack results in less significant organ damage than occurs with chronic pancreatic disease. However, a recent systematic review of cohorts of patients with acute pancreatitis found a prevalence of diabetes of 23%, and that 27 of 108 patients with diabetes following severe acute pancreatitis were using insulin if monitored beyond 5 years (17). Furthermore, a study of the prevalence of diabetes following pancreatitis or pancreatic cancer in New Zealand identified the largest cohort of cases of diabetes of the exocrine pancreas described in the literature thus far and found acute pancreatitis was the most frequent preceding disease (18). Comparison of diabetes following acute pancreatitis with both diabetes following chronic pancreatic disease and diabetes in the absence of preceding pancreatic disease would help confirm that diabetes of the exocrine pancreas routinely follows acute pancreatitis and ascertain to what extent diabetes of the exocrine pancreas is a homogenous group.

We aimed to describe the incidence of diabetes following pancreatic disease in the general population and to assess whether this patient group is more commonly classified by doctors as type 1 diabetes, as type 2 diabetes, or as diabetes of the exocrine pancreas. We also assessed whether the clinical course of diabetes following pancreatic disease differs from type 1 diabetes and type 2 diabetes by comparing trends in glycemic control and insulin use over time.

RESEARCH DESIGN AND METHODS
Study Design
We identified new diagnoses (incident cases) of diabetes and then performed a retrospective cohort study comparing those with preceding pancreatic disease to those without. Our comparative groups were adults with a new diagnosis of *A*) type 1 diabetes with no prior pancreatic disease, *B*) type 2 diabetes with no prior pancreatic disease, and *C*) diabetes following pancreatic disease, which we subdivided into *i*) diabetes following acute pancreatitis and *ii*) diabetes following chronic pancreatic disease. We report the baseline characteristics and population incidence for each group along with the diabetes classification, assigned by treating physicians, of those with diabetes following pancreatic disease. Clinical outcome measures were glycemic control and insulin use.

Setting and Data Source
We searched routinely collected electronic records from patients in England who were registered at primary care practices participating in the Royal College of General Practitioners Research and Surveillance Centre (RCGP RSC) (19). The study period was 1 January 2005 to 31 March 2016, inclusive.

The RCGP RSC extracts data once weekly from the primary care records of more than 2 million patients. All patients in the U.K. are registered with a primary care practice and have a unique National Health Service number that prevents "double-counting" in research. U.K. primary care is fully computerized. Consultations with secondary care specialists (in the large majority via the public National Health Service, but on occasion in the private sector) occurs by referral from the primary care doctor, and the specialist will write back to the primary care doctor with the findings of each consultation. The events of any acute hospital admissions are also fed back to patients' primary care practices. This information is then coded into the patient's primary care record. Data in U.K. primary care systems are encoded using Read codes. Read codes can be considered as equivalent to ICD codes but provide a more comprehensive coding system that allows the recording of diagnoses, problems, clinical findings, and treatments (20). The RCGP

RSC was initially established in 1964 for surveillance of influenza and respiratory infections (21) but has since expanded its scope to allow more detailed research.

Participants and Study Groups

Diabetes

We used Read codes to identify adults with diabetes. Adulthood was defined as age 18 years or older in accordance with national U.K. diabetes guidelines (22,23). We excluded all those whose diagnosis of diabetes preceded our study period (Read code of diagnosis before the study period, oral antihyperglycemic medication or insulin use before the study period, first diabetes Read code less than 1 year after registration at a practice). We excluded from our primary analysis those who had a conflicted coding of both type 1 and type 2 diabetes but no history of pancreatic disease but reanalyzed them as part of a secondary sensitivity analysis.

Pancreatic Disease

We also used Read codes to identify all those with a diagnosis of pancreatic disease preceding their diagnosis of diabetes. This group was subdivided into those with a history of acute pancreatitis only and those with any history of chronic pancreatic disease. The chronic conditions we identified were chronic pancreatitis, pancreatic cancer, hemochromatosis, cystic fibrosis, and surgical pancreatic resection. We included single and repeated episodes of acute pancreatitis in the acute pancreatitis group. However, a patient who was ever diagnosed with a chronic pancreatic condition before developing diabetes was included in the chronic pancreatic disease group and excluded from the acute pancreatitis group.

Baseline Characteristics and Outcome Measures

Baseline Characteristics

The baseline characteristics of age, sex, ethnicity, index of multiple deprivation score, smoking status, and BMI were extracted from the time of diagnosis of diabetes. These baseline characteristics were later adjusted for as possible confounders of glycemic control and insulin use (for which we also adjusted for HbA_{1c} at diagnosis) in the statistical models as described below.

Classification of Diabetes Following Pancreatic Disease

We examined whether those with diabetes following pancreatic disease were coded by their treating physicians as type 1 diabetes,

type 2 diabetes, or diabetes of the exocrine pancreas. Any coding containing any possible synonymous term such as "secondary pancreatic diabetes mellitus" or "secondary diabetes mellitus" we defined as consistent with a diagnosis of diabetes of the exocrine pancreas.

Glycemic Control

We extracted HbA_{1c} values at diagnosis, at 1 year, and at 5 years for each group. We used a 12-month window of 6 months before to 6 months after the 1-year and 5-year times, during which if a measurement of HbA_{1c} was made, we extracted it for analysis. We used the HbA_{1c} value closest to the desired time point when more than one value was measured in the window. We determined the number with poor glycemic control at 1 year and at 5 years. We defined poor glycemic control as $HbA_{1c} \geq 7\%$ (53 mmol/mol), according to the generic target of the American Diabetes Association and the European Association for the Study of Diabetes hyperglycemia guidelines (24). We calculated the likelihood of poor glycemic control at both 1 and 5 years for diabetes following pancreatic disease and for type 1 diabetes, with type 2 diabetes as the reference group.

Insulin Use

We assessed the number of patients who started insulin within 1 year and within 5 years of diabetes diagnosis and the proportion of those with sufficient follow-up who had started insulin at each time point. We calculated the likelihood of progression to insulin therapy for diabetes following pancreatic disease at both 1 and 5 years, with type 2 diabetes as the reference group.

Statistical Methods

We calculated incidence rates as the number of new diagnoses per the total study group person-years. We used the Pearson χ^2 test with Yates correction for continuity to test for significant differences between incidence rates, the proportion of people taking insulin, and the proportion of people with poor glycemic control (25). We created logistic regression models for odds of poor glycemic control at 1 year and at 5 years (26). To analyze time to insulin use, we produced Kaplan-Meier curves comparing type 2 diabetes without preceding pancreatic disease, diabetes following acute pancreatitis, and diabetes following chronic

pancreatic disease (27). We initially created Cox proportional hazards models to assess the hazard of progression to insulin; however, these failed proportional hazards testing (28,29). We therefore created logistic regression models for odds of progression to insulin at 1 year and 5 years. For all the statistical models we report unadjusted odds ratios and odds ratios after adjustment for baseline characteristics. Our null hypothesis for all statistical tests was that there was no difference between the compared groups, and we set a confidence level of 95% such that a P value of <0.05 would lead us to reject our null hypothesis. All statistical testing was performed using R 3.2.5 statistical software.

RESULTS

We identified 31,789 new diagnoses (incident cases) of adult-onset diabetes with a median follow-up time of 4.5 years (interquartile range [IQR] 2.0–7.4) from the date of diabetes diagnosis (Fig. 1); of these, 559 cases were of diabetes following pancreatic disease. We subdivided this group into 361 cases of diabetes following acute pancreatitis and 198 cases of diabetes following chronic pancreatic disease.

Incidence

The incidence of adult-onset diabetes following pancreatic disease was higher than the incidence of adult-onset type 1 diabetes (2.59 [95% CI 2.38–2.81] per 100,000 person-years vs. 1.64 [1.47–1.82] per 100,000 person-years; $P < 0.001$) in our population. Adult-onset type 2 diabetes had the highest incidence (142.89 [41.31–144.50] per 100,000 person-years). The proportion of diabetes following pancreatic disease among adult-onset diabetes was 1.8% compared with a proportion of 1.1% for type 1 diabetes.

Demographics

Diabetes following pancreatic disease was diagnosed at a median age of 59 years (IQR 49–70) in patients with a median BMI of 29.2 kg/m^2 (IQR 25.7–34.3). Full characteristics for each of the groups at baseline (diagnosis of diabetes) are provided in Table 1.

Classification of Diabetes Following Pancreatic Disease

Diabetes following pancreatic disease was rarely classified as diabetes of the exocrine pancreas (2.7% [95% CI 1.6–4.5]). A proportion was classified as
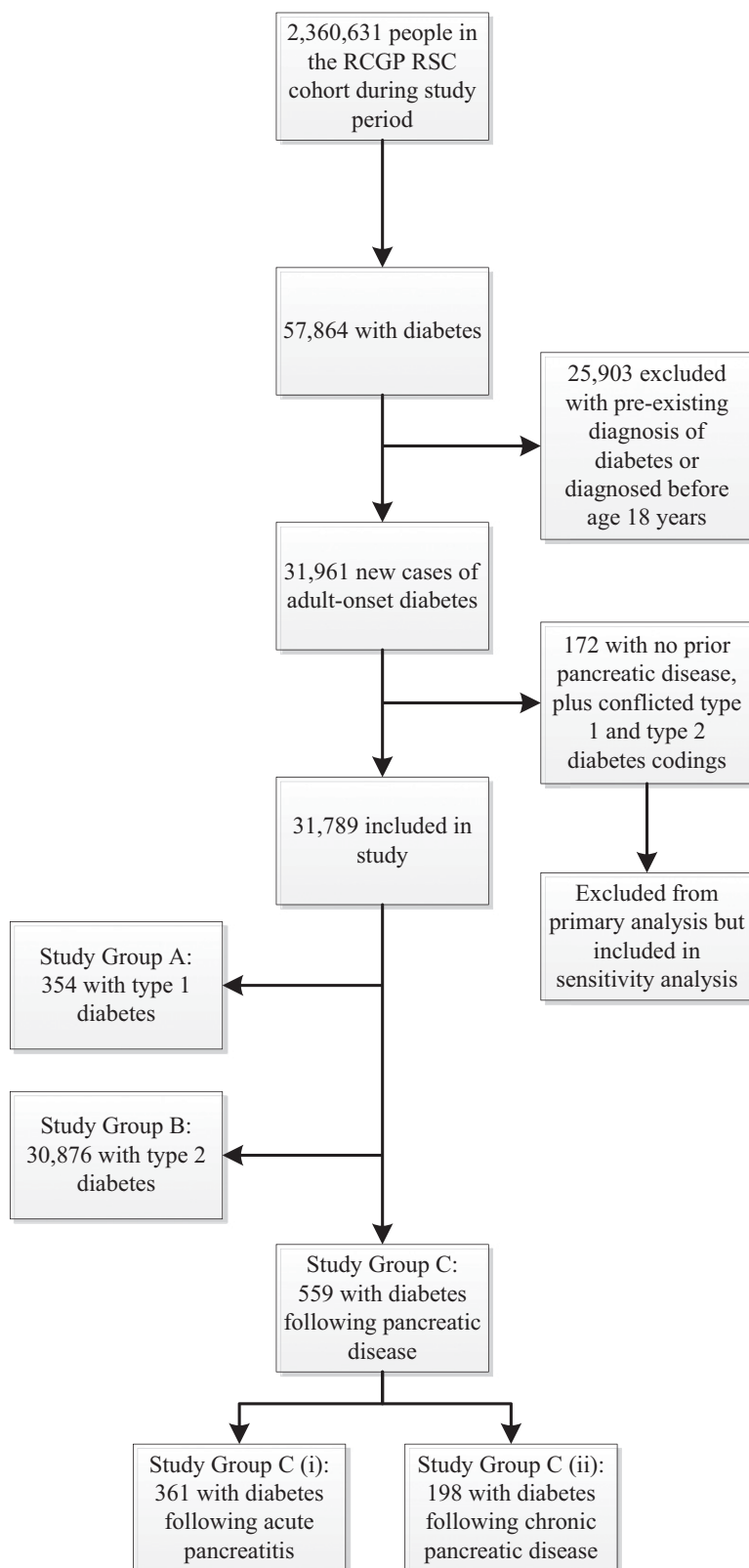
Figure 1—Identification of study groups and exclusions.

with type 2 diabetes. HbA$_{1c}$ levels were higher at presentation ($P = 0.002$) and remained higher at 1 year ($P < 0.001$) and 5 years ($P < 0.001$) after diagnosis. Mean HbA$_{1c}$ levels in people with diabetes following pancreatic disease were 8.3% (67 mmol/mol) at diagnosis, 7.1% (54 mmol/mol) at 1 year, and 7.6% (60 mmol/mol) at 5 years. Mean HbA$_{1c}$ levels in people with type 2 diabetes were 7.9% (63 mmol/mol) at diagnosis, 6.8% (51 mmol/mol) at 1 year, and 7.2% (55 mmol/mol) at 5 years. HbA$_{1c}$ levels were also higher in type 1 diabetes than in type 2 diabetes, with mean HbA$_{1c}$ levels of 12.1% (109 mmol/mol) at diagnosis, 7.6% (60 mmol/mol) at 1 year, and 8.6% (70 mmol/mol) at 5 years. Mean HbA$_{1c}$ levels in diabetes following acute pancreatitis were no different from the mean HbA$_{1c}$ levels in diabetes following chronic pancreatic disease at presentation ($P = 0.214$), at 1 year ($P = 0.642$), or at 5 years ($P = 0.779$).

People with diabetes following pancreatic disease had a greater likelihood of poor glycemic control (Supplementary Table 2) than those with type 2 diabetes. Diabetes following pancreatic disease had poor control in 40.3% (95% CI 35.7–45.1) of cases compared with 32.5% (31.9–33.1) of cases of type 2 diabetes at 1 year after diagnosis ($P < 0.001$). Diabetes following pancreatic disease had an unadjusted odds ratio for poor control at 1 year of 1.4 (1.1–1.7) compared with type 2 diabetes ($P = 0.001$). After adjustment for baseline characteristics, the odds ratio for poor control was 1.3 (1.1–1.6; $P = 0.005$). At 5 years after diagnosis, diabetes following pancreatic disease had poor control in 61.9% (54.8–68.5) of cases compared with 46.3% (45.5–47.2) of cases of type 2 diabetes ($P < 0.001$). Diabetes following pancreatic disease had an unadjusted odds ratio for poor control at 5 years of 1.7 (1.3–2.2) compared with type 2 diabetes ($P < 0.001$). After adjustment for baseline characteristics, the odds ratio for poor control was 1.7 (1.3–2.2; $P < 0.001$). People with type 1 diabetes also had worse control than those with type 2 diabetes, with adjusted odds ratios for poor glycemic control of 1.4 (1.1–1.8) at 1 year ($P = 0.007$) and 2.5 (1.7–3.7) at 5 years ($P < 0.001$).

type 1 diabetes (7.7% [5.7–10.3]), but diabetes following pancreatic disease was most commonly diagnosed as type 2 diabetes (87.8% [84.8–90.4]) (Table 2).

Glycemic Control

Mean HbA$_{1c}$ levels (Supplementary Table 1) were higher in people with diabetes following pancreatic disease than in people

Insulin Use

Diabetes following pancreatic disease was associated with early initiation of insulin therapy (Supplementary Table 3) compared

Table 1—Baseline characteristics at the time of diagnosis of diabetes

| | Diabetes with no prior pancreatic disease | | Diabetes following pancreatic disease | | |
| | Type 1 diabetes | Type 2 diabetes | All | Diabetes following acute pancreatitis | Diabetes following chronic pancreatic disease |
	n = 354	n = 30,876	N = 559	n = 361	n = 198
Age (years)					
<20	29 (8.2)	17 (0.1)	2 (0.4)	1 (0.3)	1 (0.5)
20–29	96 (27.1)	226 (0.7)	17 (3.0)	8 (2.2)	9 (4.5)
30–39	103 (29.1)	1,284 (4.2)	38 (6.8)	22 (6.1)	16 (8.1)
40–49	65 (18.4)	4,517 (14.6)	85 (15.2)	52 (14.4)	33 (16.7)
50–59	36 (10.2)	7,546 (24.4)	147 (26.3)	90 (24.9)	57 (28.8)
60–69	18 (5.1)	8,727 (28.3)	123 (22.0)	80 (22.2)	43 (21.7)
70–79	5 (1.4)	6,141 (19.9)	94 (16.8)	64 (17.7)	30 (15.2)
≥80	2 (0.6)	2,418 (7.8)	53 (9.5)	44 (12.2)	9 (4.5)
Sex					
Female	129 (36.4)	13,490 (43.7)	230 (41.1)	157 (43.5)	73 (36.9)
Male	225 (63.6)	17,386 (56.3)	329 (58.9)	204 (56.5)	125 (63.1)
Ethnicity					
Asian	9 (2.5)	2,148 (7.0)	21 (3.8)	16 (4.4)	5 (2.5)
Black	7 (2.0)	921 (3.0)	8 (1.4)	4 (1.1)	4 (2.0)
Mixed	1 (0.3)	229 (0.7)	2 (0.4)	2 (0.6)	0 (0.0)
Other	1 (0.3)	230 (0.7)	3 (0.5)	2 (0.6)	1 (0.5)
White	244 (68.9)	22,248 (72.1)	430 (76.9)	276 (76.5)	154 (77.8)
Unknown	92 (26.0)	5,100 (16.5)	95 (17.0)	61 (16.9)	34 (17.2)
IMD score					
First quintile	82 (23.2)	7,298 (23.6)	126 (22.5)	88 (24.4)	38 (19.2)
Second quintile	86 (24.3)	6,778 (22.0)	109 (19.5)	70 (19.4)	39 (19.7)
Third quintile	62 (17.5)	5,382 (17.4)	87 (15.6)	52 (14.4)	35 (17.7)
Fourth quintile	51 (14.4)	5,636 (18.3)	109 (19.5)	71 (19.7)	38 (19.2)
Fifth quintile	69 (19.5)	5,595 (18.1)	125 (22.4)	78 (21.6)	47 (23.7)
Unknown	4 (1.1)	187 (0.6)	3 (0.5)	2 (0.6)	1 (0.5)
Alcohol consumption*					
None	61 (17.2)	8,634 (28.0)	145 (25.9)	105 (29.1)	40 (20.2)
Safe	105 (29.7)	6,755 (21.9)	107 (19.1)	71 (19.7)	36 (18.2)
Hazardous	112 (31.6)	12,510 (40.5)	177 (31.7)	121 (33.5)	56 (28.3)
Alcoholic	21 (5.9)	1,425 (4.6)	103 (18.4)	49 (13.6)	54 (27.3)
Unknown	55 (15.5)	1,552 (5.0)	27 (4.8)	15 (4.2)	12 (6.1)
Smoking status					
Never smoked	122 (34.5)	7,280 (23.6)	100 (17.9)	60 (16.6)	40 (20.2)
Former smoker	138 (39.0)	19,310 (62.5)	318 (56.9)	217 (60.1)	101 (51.0)
Current smoker	94 (26.6)	4,224 (13.7)	140 (25.0)	84 (23.3)	56 (28.3)
Unknown	0 (0.0)	62 (0.2)	1 (0.2)	0 (0.0)	1 (0.5)
BMI (kg/m^2)					
<18.5	11 (3.1)	59 (0.2)	9 (1.6)	0 (0.0)	9 (4.5)
≥18.5–24.9	107 (30.2)	2,242 (7.3)	84 (15.0)	40 (11.1)	44 (22.2)
≥25–29.9	47 (13.3)	7,451 (24.1)	130 (23.3)	89 (24.7)	41 (20.7)
≥30.0	35 (9.9)	14,886 (48.2)	196 (35.1)	151 (41.8)	45 (22.7)
Unknown	154 (43.5)	6,238 (20.2)	140 (25.0)	81 (22.4)	59 (29.8)
HbA$_{1c}$ (%) [mmol/mol]					
<7.0 [<53]	3 (0.8)	10,500 (34.0)	170 (30.4)	114 (31.6)	56 (28.3)
≥7.0–7.9 [≥53–63]	8 (2.3)	5,740 (18.6)	94 (16.8)	64 (17.7)	30 (15.2)
≥8.0–8.9 [≥64–74]	4 (1.1)	2,030 (6.6)	32 (5.7)	26 (7.2)	6 (3.0)
≥9.0–9.9 [≥75–85]	15 (4.2)	1,344 (4.4)	31 (5.5)	17 (4.7)	14 (7.1)
≥10.0–10.9 [≥86–96]	20 (5.6)	1,186 (3.8)	23 (4.1)	17 (4.7)	6 (3.0)
≥11.0–11.9 [≥97–107]	33 (9.3)	1,018 (3.3)	24 (4.3)	12 (3.3)	12 (6.1)
≥12.0 [≥108]	85 (24.0)	1,381 (4.5)	43 (7.7)	23 (6.4)	20 (10.1)
Unknown	186 (52.5)	7,677 (24.9)	142 (25.4)	88 (24.4)	54 (27.3)

Data are presented as n (%). Groups are split into type 1 diabetes with no prior history of pancreatic disease, type 2 diabetes with no prior history of pancreatic disease, and diabetes that developed following pancreatic disease. Diabetes following pancreatic disease is subdivided into diabetes following acute pancreatitis and diabetes following any chronic pancreatic disease. IMD, index of multiple deprivation. *Alcohol consumption was divided into four categories based on Read code data: "none" (current nondrinker), "safe" (<14 units per week or only occasional consumption), "hazardous" (>14 units per week or excess consumption), or "alcoholic" (alcohol-related disease complications or alcoholism treatment).

Table 2—Classification of diabetes by clinicians, for diabetes that developed following pancreatic disease

Classification of diabetes	All	Diabetes following pancreatic disease	
		Diabetes following acute pancreatitis	Diabetes following chronic pancreatic disease
Coding consistent with type 1 diabetes	43 (7.7)	14 (3.9)	29 (14.6)
Coding consistent with type 2 diabetes	491 (87.8)	336 (93.1)	155 (78.3)
Conflicted type 1 and type 2 diabetes codes	10 (1.8)	2 (0.6)	8 (4.0)
Coding consistent with diabetes of the exocrine pancreas	15 (2.7)	9 (2.5)	6 (3.0)
Total	559 (100)	361 (100)	198 (100)

Data are presented as n (%).

with type 2 diabetes. At 1 year after diagnosis, 1.4% (95% CI 1.3–1.6) of those with type 2 diabetes required insulin, rising to 4.1% (3.8–4.4) at 5 years. In comparison, insulin use in diabetes following pancreatic disease was 16.3% (13.1–20.0) at 1 year ($P < 0.001$), rising to 29.6% (23.6–36.4) at 5 years ($P < 0.001$). Diabetes following pancreatic disease had an unadjusted odds ratio for insulin use at 1 year of 13.5 (10.3–17.5) compared with type 2 diabetes ($P < 0.001$). After adjustment for baseline characteristics, the odds ratio for insulin use was 9.6 (7.0–13.2; $P < 0.001$). Diabetes following pancreatic disease had an unadjusted odds ratio for insulin use at 5 years of 9.9 (7.2–13.4) compared with type 2 diabetes ($P < 0.001$). After adjustment for baseline characteristics, the odds ratio for insulin use was 7.4 (5.2–10.4; $P < 0.001$).

Diabetes following chronic pancreatic disease had a higher rate of insulin use than diabetes following acute pancreatitis (Fig. 2); however, patients in both of these subgroups had a greater requirement for insulin than those with type 2 diabetes (Supplementary Table 3). At 1 year after diagnosis, 9.7% (95% CI 6.8–13.7) of those with diabetes following acute pancreatitis were using insulin, rising to 20.9% (14.6–28.9) at 5 years. At 1 year after diagnosis, 28.9% (22.2–36.7) of those with diabetes following chronic pancreatic disease were using insulin, rising to 45.8% (34.2–57.9) at 5 years (all $P < 0.001$ compared with type 2 diabetes).

Supplementary Analyses
A summary of the patient characteristics and outcomes further subdivided by individual pancreatic diseases is provided in Supplementary Table 4. We also performed a sensitivity analysis that demonstrated that inclusion of patients with conflicted type 1 and type 2 diabetes diagnoses did not affect our findings (data not shown).

CONCLUSIONS

Diabetes following pancreatic disease is frequently labeled type 2 diabetes but follows a different clinical course, with worse glycemic control and a markedly greater requirement for insulin. This is the largest study to include all forms of diabetes of the exocrine pancreas to date, and to our knowledge, the only study to systematically identify pancreatic disease in a cohort of people with newly diagnosed diabetes.

We show that diabetes following pancreatic disease has a higher incidence in adults than type 1 diabetes. We were unable to find any other primary evidence comparing the incidence, prevalence, or demographics of diabetes of the exocrine pancreas with type 1 or type 2 diabetes in the general population. This finding, however, is in keeping with a large epidemiological study of the prevalence of diabetes of the exocrine pancreas in New Zealand, in which the researchers hypothesized that
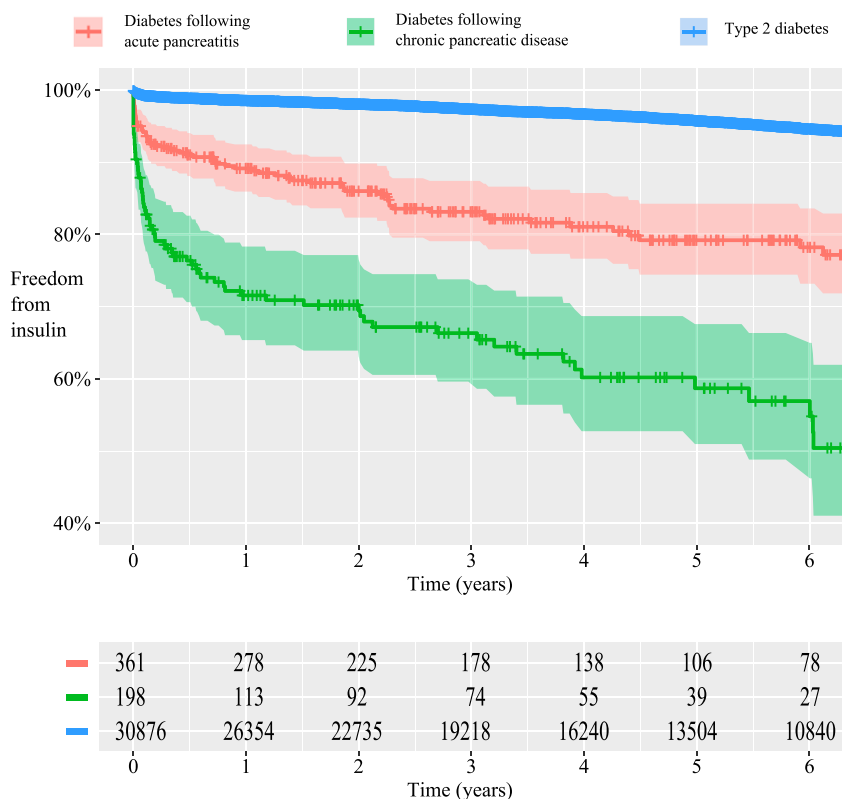
Figure 2—Kaplan-Meier curves of freedom from insulin use over time for type 2 diabetes, diabetes following acute pancreatitis, and diabetes following chronic pancreatic disease. The shaded areas represent the 95% CIs. Log-rank P for difference: $P < 0.001$. The table is the number of patients at risk over time.

at a rate of 1.13 per 1,000 general population, the prevalence of diabetes of the exocrine pancreas may be not dissimilar to type 1 diabetes (18).

Important limitations when interpreting our findings are the retrospective collection of data and the use of Read codes to identify pancreatic disease and to classify diabetes. This method can result in misclassification and selection bias (30). The RCGP RSC has been shown to be a source of high-quality data and is representative of the population of England (19). However generalizability of our data to other countries may be limited, especially in those with a different burden of pancreatic disease. This is of particular significance when considering ethnic groups of low prevalence in the U.K. For example, Pendharkar et al. (31) found people of Māori and Pacific ethnicity had an incidence of diabetes following pancreatitis that was three times that of people with New Zealand European ethnicity. It is likely that our findings regarding the glycemic control and insulin requirements of those with diabetes following pancreatic disease relate to the pathophysiology of diabetes of the exocrine pancreas and so can be generalized. A limitation of these findings is the varied availability of HbA_{1c} data for patients. Data were missing for 13.6% of cases of diabetes following pancreatic disease at 1 year and for 13.7% of cases at 5 years (Supplementary Table 1). The absence of HbA_{1c} data were adjusted for as a potential confounder in the logistic regression models.

Our study indicates that many people with diabetes of the exocrine pancreas are currently misdiagnosed. We found that only 2.7% of people with diabetes following pancreatic disease are diagnosed with diabetes of the exocrine pancreas. Most patients were labeled type 2 diabetes, despite a sevenfold increased insulin requirement within 5 years, by which time 45.8% of patients with diabetes following chronic pancreatic disease are using insulin. Ewald et al. (1) used diagnostic criteria, including the presence of both exocrine pancreatic dysfunction and pathological pancreatic imaging, to retrospectively identify diabetes of the exocrine pancreas in their hospital's inpatients and found 49% were initially misclassified. Whether all diabetes that develops following pancreatic disease should be managed according to recommendations for diabetes of the exocrine pancreas (32) or

whether some patients would be appropriate for standard type 1 or type 2 diabetes management pathways is an area that requires further study. In our population, people with type 2 diabetes and people with diabetes following pancreatic disease were both most frequently diagnosed with diabetes between the ages of 50 and 69 years and at a BMI ($\geq$30.0 kg/m^2) compatible with obesity. This may partially explain why diabetes of the exocrine pancreas is often mistaken for type 2 diabetes. However, a higher percentage of people with diabetes following pancreatic disease were diagnosed when younger than 50 years old and at a BMI compatible with being underweight ($<$18.5 kg/m^2) or at a healthy weight ($\geq$18.5–24.9 kg/m^2), and it is not possible to tell from our retrospective study whether diagnosis was more common at higher age and BMI because this was the context in which diabetes first developed, or because of another factor such as more frequent screening for diabetes in that demographic.

Acute pancreatitis was the most common pancreatic disease preceding diabetes in our population. This may be the result of a higher background prevalence of acute pancreatitis than the other pancreatic diseases. Considering the variety of pathological processes that cause pancreatic injury, diabetes of the exocrine pancreas is likely to be heterogeneous in nature. Patients may lie along a spectrum ranging from those with an underlying predisposition toward type 2 diabetes, in whom an additional pancreatic insult becomes diabetogenic, to those in whom a total pancreatectomy removes all endogenous insulin production. There is some evidence that the greater the severity of pancreatic damage the greater the failure of insulin production (33,34). In our study, diabetes following acute pancreatitis displayed HbA_{1c} levels equivalent to those of diabetes following chronic pancreatic disease but was associated with a lower rate of insulin use. A possible explanation for this could be that although acute pancreatitis alters insulin production (33), diabetes following acute pancreatitis involves comparatively less failure of insulin production and more insulin resistance than diabetes following chronic pancreatic disease. One study of acute pancreatitis found HOMA-insulin resistance levels (a calculation of insulin resistance) had a stronger association

with the presence of prediabetes or diabetes than did the HOMA-%β reduction (a calculation of β-cell function) (35). We note that the pathways that result in type 1 diabetes, type 2 diabetes, and diabetes of the exocrine pancreas need not be mutually exclusive. When adipocytokines implicated in the development of type 2 diabetes were studied as a possible mechanism for chronic hyperglycemia after acute pancreatitis, a suggested role was found for interleukin-6 (36). Clinical differences should not be disregarded, however, because we found diabetes following acute pancreatitis had significantly worse glycemic control (at 1 year and 5 years) and higher rates of insulin prescription than type 2 diabetes.

The combination of increased likelihood of poor glycemic control and accelerated requirement for insulin suggests that patients with diabetes following pancreatic disease may benefit from more frequent review than is normally necessitated in type 2 diabetes. Given the complexity of both classifying and managing diabetes following pancreatic disease, these patients may benefit from management in a specialist setting or with multidisciplinary dietitian and gastroenterology input. However, it is not possible from our observational study to draw inferences about whether the increased likelihood of poor glycemic control could be prevented with more frequent recognition of diabetes of the exocrine pancreas or whether comparatively poor glycemic control is unavoidable as a result of the underlying pathophysiology. Interventional studies may help to elucidate the risk-benefit profile of various antihyperglycemic agents and whether more frequent review reduces complications or hospitalizations.

In summary, diabetes that develops following pancreatic disease is significantly associated with poor glycemic control and early insulin therapy but is rarely identified as diabetes of the exocrine pancreas. Clinicians should elicit whether a patient has any history of pancreatic disease when they first present with diabetes and consider the diagnosis of diabetes of the exocrine pancreas. Diabetes of the exocrine pancreas must be appropriately recognized to tailor management, including choice of antihyperglycemic therapy, and consideration of malabsorption requiring pancreatic enzyme and vitamin D prescription. Greater awareness

of diabetes of the exocrine pancreas is required to appropriately manage this diabetes subgroup.

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