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Clinical and biochemical characteristics of postpancreatitis diabetes mellitus: A cross-sectional study from the Danish nationwide DD2 cohort

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Abstract

Background: Postpancreatitis diabetes mellitus (PPDM) is a common metabolic sequalae of acute and chronic pancreatitis. We conducted a cross-sectional study to examine the proportion of PPDM among patients clinically diagnosed with type 2 diabetes (T2D) in Denmark and their clinical and biochemical characteristics.

Methods: We identified all past diagnoses of pancreatitis among patients in the Danish Centre for Strategic Research in Type 2 Diabetes (DD2) cohort through linkage with national health registries. Using *International Classification of Diseases, Tenth Revision* codes we categorized patients as PPDM and further divided them into acute/chronic subtypes (PPDM-A and PPDM-C). We assessed PPDM prevalence and examined associations with *clinical and biochemical parameters* using log binomial or Poisson regression to calculate age-/sex-adjusted prevalence ratios (aPRs).

Results: Among 5564 patients with a clinical diagnosis of T2D, 78 (1.4%) had PPDM. Compared to T2D, PPDM patients were more often underweight or normal weight (body mass index ≤25.0 kg/m^2: aPR 2.3; 95% confidence interval [CI]: 1.6-3.2) and had lower waist-to-hip ratio (≤0.95/≤0.80 in men/women: aPRs 1.8; 95% CI: 1.2-2.7). PPDM patients had lower plasma amylase levels (<17 U/L: aPRs 2.2; 95% CI: 1.1-4.3), higher insulin sensitivity (homeostatic model assessment 2S [HOMA2S] >63: aPR 2.0; 95% CI: 1.2-3.2) and tended to have worse glycaemic control (HbA1c ≥8.0%: aPRs 1.4; 95% CI: 0.8-2.4). PPDM-A was largely indistinguishable from T2D, whereas PPDM-C had impaired insulin secretion, higher insulin sensitivity, and worse glycemic control.

Conclusions: The proportion of PPDM among patients with clinically diagnosed T2D is ~1.5% in an everyday clinical care setting. Glucose metabolism of

PPDM-A is largely indistinguishable from T2D, whereas PPDM-C differs in relation to insulin secretion and sensitivity.

KEYWORDS

beta-cell function, glucose homeostasis, insulin resistance, plasma amylase, prevalence

Highlights

- Among patients with clinically diagnosed type 2 diabetes, the proportion of postpancreatitis diabetes mellitus (PPDM) is ~1.5% in an everyday clinical care setting.
- Glucose metabolism of PPDM folowing acute pancreatitis is largely indistinguishable from T2D, whereas PPDM associated with chronic pancreatitis differs in relation to insulin secretion, insulin sensitivity, and glycemic control.

1 | INTRODUCTION

Diabetes is a common metabolic sequela of pancreatic diseases and constitutes a heterogeneous condition resulting from diverse etiological mechanisms.[1,2] The term "diabetes of the exocrine pancreas" is used to classify this type of secondary diabetes according to the most recent version of the American Diabetes Association "Standards of Medical Care in Diabetes."[3,4] In addition to acute and chronic pancreatitis, etiologies also include pancreatic neoplasia, cystic fibrosis, pancreatectomy, hemochromatosis, and trauma.[1-3] Postpancreatitis diabetes mellitus (PPDM) accounts for ~80% of all cases of diabetes of the exocrine pancreas and recent data indicate that PPDM may constitute ~1%-2% of all adult diabetes cases.[5,6] This makes PPDM one of the most common types of adult-onset diabetes after type 2 diabetes (T2D).[5,6]

Although an increased research focus has been directed toward PPDM since its original classification, PPDM has not been widely recognized as a distinct condition in the clinical setting where the majority of cases are classified and treated as T2D.[1,6] However, diagnosing and treating PPDM as T2D is problematic, as PPDM may be characterized by different pathophysiological mechanisms and needs special attention and management because of increased risk of complications and excess mortality.[7,8] Individuals with PPDM seem to have a higher risk of all-cause mortality, worse glycemic control, and higher risk of hospitalization compared with T2D.[6-8] In addition, glucose-lowering medications (such as metformin and insulin) may have a different benefit-risk balance in PPDM vs T2D and the widely used incretin-based therapies should be used with caution in patients with a history of pancreatitis.[9-12] Currently there are no guidelines available for the diagnosis and management of PPDM and their development is hampered by an incomplete understanding of the underlying pathophysiology.[5,11]

Past studies indicate that PPDM is a heterogeneous entity caused by multiple pathophysiological mechanisms.[13] In the setting of chronic pancreatitis, diabetes has historically been attributed to loss of beta-cell following pancreatic damage leading to decreasing insulin secretion (PPDM-C).[11] However, recent studies indicate that other mechanisms are operative, including hereditary and other known risk factors for classical T2D.[14-16] The pathophysiology behind PPDM following acute pancreatitis (PPDM-A) is similarly multifaceted and may include insulin resistance mediated by sustained low-grade inflammation, beta-cell compensation, and hyperinsulinemia.[13] Furthermore, anecdotal data suggest that attacks of pancreatitis may trigger an autoimmune response directed at the pancreas thus resembling the pathophysiology of type 1 diabetes.[17]

The majority of past studies of PPDM have focused on single pathophysiological mechanisms using biomarkers not commonly available outside research environments. Also, most previous studies of PPDM did not examine measures of glucose metabolism or autoimmunity, and few studies compared characteristics of PPDM patients with a group of T2D patients. We therefore conducted a large cross-sectional study of patients with recent onset diabetes prospectively enrolled in the Danish Centre for Strategic Research in Type 2 Diabetes (DD2) cohort and used routine clinical and biochemical parameters, including measures of glucose metabolism and autoimmunity, to characterize patients with PPDM and compared them to patients with T2D.

We hypothesized that patients with PPDM and its acute/chronic subtypes (PPDM-A and PPDM-C) have distinct clinical and biochemical characteristics compared to patients with T2D. The aims of the study were (a) to investigate the proportion of PPDM and its subtypes among patients enrolled with recently onset clinically diagnosed T2D in a large cohort in Denmark and (b) to characterize patients with PPDM using routine clinical, anthropometric, lifestyle, and biochemical parameters, including measures of glucose metabolism and autoimmunity, and compare them to patients with T2D.

2 | METHODS

2.1 | Study design and data sources

This was a cross-sectional study based on baseline data from the DD2 cohort. The DD2 has enrolled patients with recent onset clinically diagnosed T2D patients from general practitioners and hospital specialist outpatient clinics since 2010. All patients with a clinical diagnosis of T2D, as judged by the healthcare provider, are eligible for enrolment irrespective of use or type of glucose-lowering treatment. Participants undergo a detailed interview and clinical examination at enrolment and provide blood and urine samples for biobanking. A detailed description of the DD2 methodology is provided elsewhere.[18,19]

Information on patients' past history of acute or chronic pancreatitis was obtained through linkage with the Danish National Patient Registry (DNPR). This is a nationwide registry that covers all nonpsychiatric hospital admissions since 1977 and all outpatient clinic and emergency room contacts since 1995. Data include relevant dates and discharge diagnoses coded according to the *International Classification of Diseases, Tenth Revision* (ICD-10) since 1994.[20] Information on glucose lowering therapies and glucocorticoid prescription (to identify cases with possible glucocorticoid associated diabetes) was obtained from the Danish National Health Service Prescription Registry.[21]

This study was approved by the by the National Committee on Health Research Ethics (Denmark) (record number S-20100082) and the Danish Data Protection Agency (record number 2008-58-0035). After receiving detailed oral and written information all cohort participants gave written informed consent.

2.2 | Study cohort

The study base comprised 8190 individuals with recent onset clinically diagnosed T2D enrolled in the DD2 study cohort between 30 November 2010 and 20 August 2018. Glutamic acid decarboxylase (GAD) antibodies and C-peptide were analyzed among the first 5720 consecutive patients enrolled and we excluded the remaining 2470 patients with no available measurements of GAD and C-peptide, because these measurements were needed to exclude the presence of type 1 diabetes based on previously published criteria (GAD $\geq$20 IU/mL and age <30 years and C-peptide level $\leq$300 pmol/L).[22] In addition, 17 patients with rare forms of diabetes were excluded and another 39 patients were excluded because of glucocorticoid associated diabetes.[22] This left 5564 patients eligible for further phenotyping into either T2D or PPDM as defined subsequently (Figure 1). In order to investigate if patients with PPDM had an increased prevalence of GAD-antibody positivity, as indicated by recent case studies,[17] we did not exclude patients who were GAD-antibody positive unless they matched the definition of type 1 diabetes. This may have resulted in the inclusion of a few patients with latent autoimmune diabetes of adulthood (LADA) in the T2D group.

2.3 | Definition and classification of PPDM

The definition and classification of PPDM followed a previously published algorithm.[5] Patients with a history of acute or chronic pancreatitis were identified based on data from the DNPR using ICD-10 code K85 for acute pancreatitis and ICD-10 codes K86.0, K86.1 for chronic pancreatitis. These codes have a positive predictive value of 93% for acute pancreatitis and 80% for chronic pancreatitis in the Danish registers.[23] Patients were defined as PPDM cases if they had had a diagnosis of acute or chronic pancreatitis more than 3 months before the onset of diabetes.[5] After defining the PPDM cases these were further classified in two groups based on patients´ past history of acute pancreatitis (PPDM-A) or chronic pancreatitis (PPDM-C). Patients who had a preceding diagnosis of both acute and chronic pancreatitis were classified only as PPDM-C and not PPDM-A.

2.4 | Demographic, anthropometric, and clinical parameters

We extracted data on age, gender, hip and waist circumference, family history of diabetes, and alcohol intake from the DD2 core database. From linked medical and administrative registries we had additional information on tobacco smoking and weight, height, and body mass index (BMI) for a subgroup of DD2 patients.[18] Hip and waist circumference and BMI were divided into clinically relevant categories. Patients with underweight (BMI

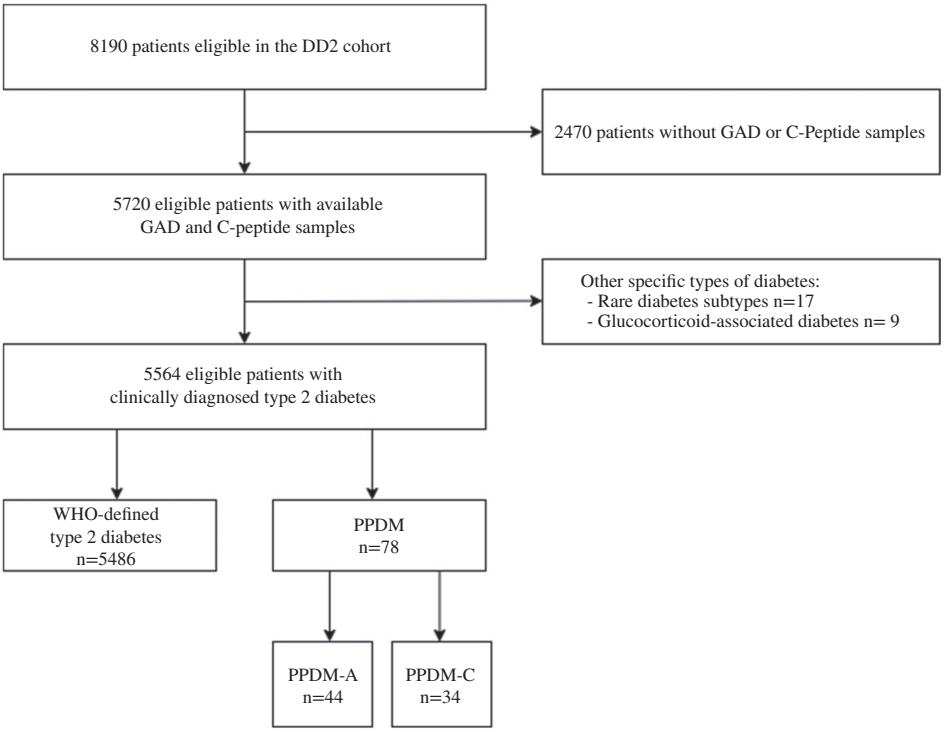

FIGURE 1 Study flowchart. Abbreviations: DD2, Danish Centre for Strategic Research in Type 2 Diabetes; GAD, glutamic acid decarboxylase; PPDM-A, postpancreatitis diabetes mellitus following acute pancreatitis; PPDM-C, postpancreatitis diabetes mellitus asssocaited with chronic pancreatitis; WHO, World Health Organization

<18.5 kg/m^2) and normal weight (BMI 18.5-25.0 kg/m^2) were grouped owing to a low number of individuals in the underweight group.

2.5 | Biochemical parameters

All biochemical tests using blood samples from the DD2 biobank were performed in the laboratory at Centre Hospital Lillebaelt, Region of Southern Denmark. The laboratory is accredited according to the International Organization for Standardization 15189 standard. Fasting C-peptide was analyzed using the Roche C-Peptide assay (Roche Diagnostics, Mannheim, Germany) and fasting plasma glucose was analyzed using an enzymatic hexokinase method (Glucoquant Glucose/HK, Roche Diagnostics, Mannheim, Germany). We used version 2 of the revised homeostatic assessment model (HOMA2) to estimate insulin sensitivity (HOMA2S) and beta cell function (HOMA2B) based on fasting plasma glucose values and C-peptide.[24] HOMA2 parameters were categorized according to previously published thresholds.[22] We analyzed GAD-antibodies using the AESKULISA GAD65 kit (AESKU Diagnostics, Wendelsheim, Germany). Pancreas specific amylase was analyzed for the first 996 consecutive patients enrolled in the DD2 cohort using the COBAS-6000 analyzer produced by Roche Diagnostics GmbH, Mannheim, Germany. A cutoff <17 U/L was used to define patients with a low amylase level.[25] The remaining biochemical parameters (triglycerides, HbA1c, and urine albumin/creatinine ratio) were collected from linked medical and administrative registries.[18]

2.6 | Statistics

Using prevalence ratios for each category, we compared the populations of all PPDM, PPDM-A, and PPDM-C patients to T2D patients. We obtained crude prevalence ratios (PR) and adjusted prevalence ratios (aPR, adjusting for age and sex) for different characteristics, using log-binomial regression when the model converged, and Poisson regression with robust variance in case of non-convergence. In a subanalysis of HOMA2 parameters we also adjusted the PRs for waist-to-hip ratios to investigate the influence of central obesity on glucose metabolism. We made a plot of HOMA2B (beta cell function) against HOMA2S (insulin sensitivity) to graphically evaluate the difference of these between PPDM and T2D patients. All statistical analyses were conducted using SAS version 9.4 (SAS Institute Inc, Cary, NC).

3 | RESULTS

A diagram illustrating the patient inclusion flow is presented in Figure 1. In total 5664 patients with recent clinically diagnosed T2D were eligible for this study of whom 58.5% were men (Table 1). The median age was 62.2 years (interquartile range [IQR] 53.3-68.7). Among included

TABLE 1 Demographic and clinical characteristics of patients with WHO-defined type 2 diabetes (T2D) and postpancreatitis diabetes mellitus (PPDM)

	All (n = 5564)	T2D (n = 5486)	PPDM (n = 78)
Age, y (IQR)	62.2 (53.3; 68.7)	62.2 (53.3; 68.8)	61.8 (53.0; 67.3)
Age category, n (%)			
<40 y	228 (4.1)	227 (4.1)	<5
40-49 y	715 (12.9)	701 (12.8)	14 (17.9)
50-59 y	1414 (25.4)	1398 (25.5)	16 (20.5)
60-69 y	2055 (36.9)	2020 (36.8)	35 (44.9)
70-79 y	1006 (18.1)	996 (18.2)	10 (12.8)
≥80 y	146 (2.6)	144 (2.6)	<5
Men, n (%)	3257 (58.5)	3205 (58.4)	52 (66.7)
Women, n (%)	2307 (41.5)	2281 (41.6)	26 (33.3)
Family history of T2D, n (%)			
Yes	2927 (52.6)	2891 (52.7)	36 (46.2)
No	2142 (38.5)	2107 (38.4)	35 (44.9)
Unknown	495 (8.9)	488 (8.9)	7 (9.0)
Parents with T2D, n (%)			
Yes	1938 (34.8)	1914 (34.9)	24 (30.8)
No/unknown	3626 (65.2)	3572 (65.1)	54 (69.2)
Median weight, kg (IQR)	90.0 (79.0;104.0)	90.0 (79.0;104.0)	81.5 (70.0;90.0)
Median height, cm (IQR)	172.5 (165.0;179.0)	172.8 (165.0;179.0)	172.0 (165.0;178.0)
BMI, kg/m^2 (IQR)	30.1 (26.9;34.2)	30.2 (26.9;34.2)	27.5 (23.8;32.3)
BMI category, n (%)			
<18.5	11 (0.2)	8 (0.1)	<5
18.5-25	683 (12.3)	663 (12.1)	20 (25.6)
25-30	1802 (32.4)	1778 (32.4)	24 (30.8)
>30	2639 (47.4)	2614 (47.6)	25 (32.1)
Missing	429 (7.7)	423 (7.7)	6 (7.7)
Median hip circumference, cm (IQR)	107.0 (101.0;116.0)	107.0 (101.0;116.0)	102.0 (95.0;113.0)
Median waist circumference, cm (IQR)	106.0 (97.0;116.0)	106.0 (97.0;116.0)	102.5 (90.0;114.0)
Waist/hip ratio (men/women), n (%)			
≤0.95/≤0.80	636 (11.4)	619 (11.3)	17 (21.8)
0.96-1.0/0.81-0.85	1163 (20.9)	1147 (20.9)	16 (20.5)
>1.0/>0.85	3757 (67.5)	3712 (67.7)	45 (57.7)
Unknown	8 (0.1)	8 (0.1)	0 (0.0)
Smoking status, n (%)			
Unknown	1086 (19.5)	1068 (19.5)	18 (23.1)
Never smoked	2085 (37.5)	2063 (37.6)	22 (28.2)
Ex-smoker	1529 (27.5)	1512 (27.6)	17 (21.8)
Smoke daily	815 (14.6)	795 (14.5)	20 (25.6)
Smoke occasionally	49 (0.9)	48 (0.9)	<5
Alcohol consumption (women/men), n (%)			
Drink less than 14 units/21 units weekly	5181 (93.1)	5106 (93.1)	75 (96.2)
Drink more than 14 units/21 units weekly	383 (6.9)	380 (6.9)	<5

(Continues)

TABLE 1 (Continued)

	All (n = 5564)	T2D (n = 5486)	PPDM (n = 78)
Glucose lowering therapy, n (%)			
Any glucose lowering therapy	4298 (77.2)	4236 (77.2)	62 (79.5)
Insulins	298 (5.4)	281 (5.1)	17 (21.8)
Biguanides	4047 (72.7)	3998 (72.9)	49 (62.8)
DPP-4 inhibitors	382 (6.9)	376 (6.9)	6 (7.7)
GLP-1 receptor agonists	252 (4.5)	251 (4.6)	<5
SGLT-2 inhibitors	23 (0.4)	22 (0.4)	<5
Sulfonylureas	280 (5.0)	272 (5.0)	8 (10.3)

Abbreviations: BMI, body mass index; DPP4, dipeptidyl peptidase 4 inhibitors; GLP-1, glucagon-like peptide-1; IQR, interquartile range; SGLT-2, sodium-glucose cotransporter-2; WHO, World Health Organization.

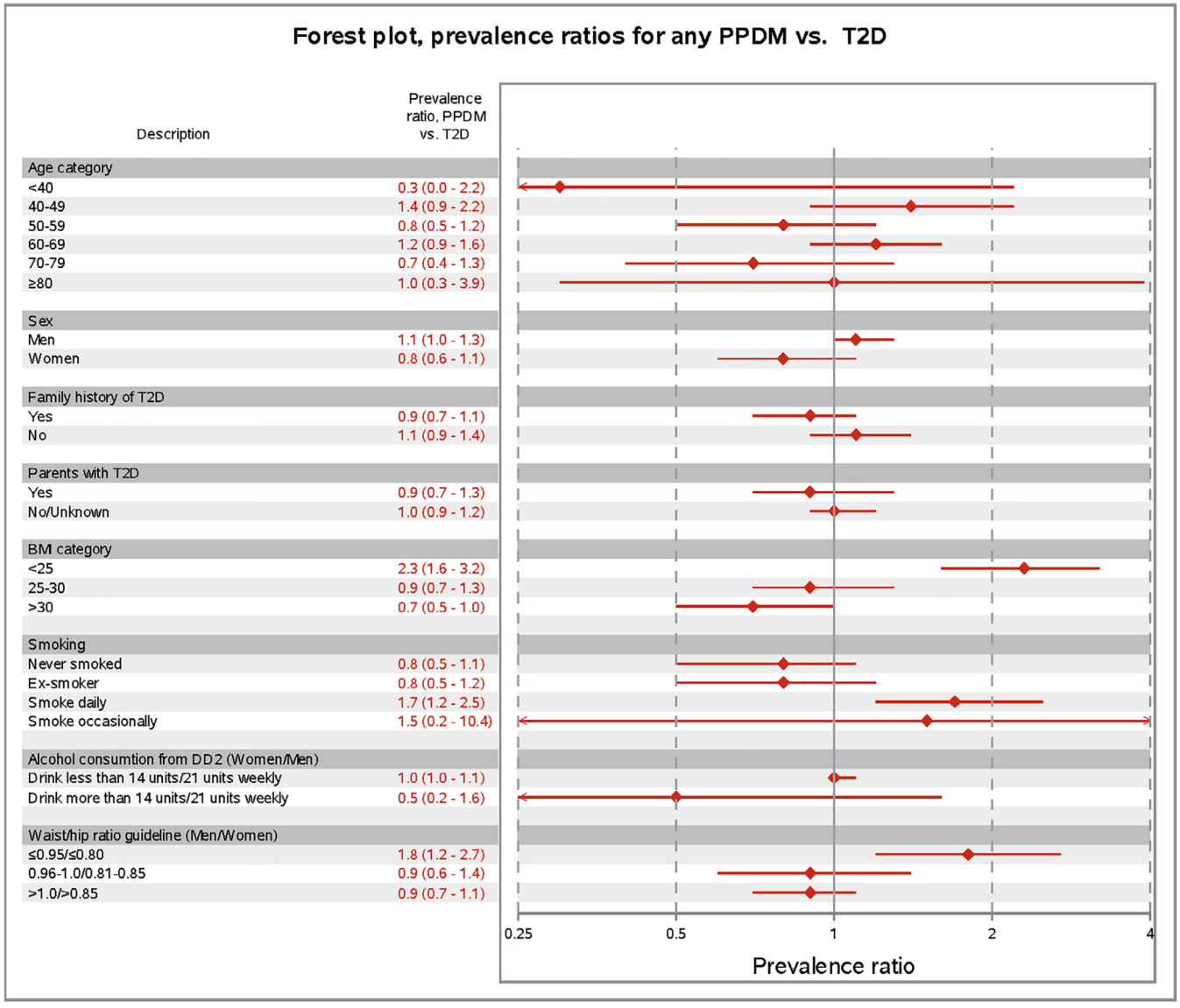

FIGURE 2 A, Age- and sex-adjusted prevalence ratios of demographic and clinical parameters for PPDM vs T2D. B, Age- and sex-adjusted prevalence ratios of biochemical parameters for PPDM vs T2D. Abbreviations: BMI; Body Mass Index, DD2, Danish Centre for Strategic Research in Type 2 Diabetes; GAD, glutamic acid decarboxylase; HOMA, homeostatic assessment model; PPDM, postpancreatitis diabetes mellitus; T2D, type 2 diabetes

patients, 5486 (98.6%) were classified as T2D and 78 (1.4%) were classified as PPDM. Among PPDM patients 44 (56%) had a prior diagnosis of acute pancreatitis (PPDM-A) and 34 (44%) had chronic pancreatitis (PPDM-C).

3.1 | Characteristics of PPDM vs T2D

Demographic and clinical characteristics of patients with PPDM and T2D are reported in Table 1 and the corresponding aPRs are shown in Figure 2A. Compared to patients with T2D, PPDM patients were more often normal weight or underweight (BMI ≤25.0 kg/m^2: aPR 2.3; 95% confidence interval [CI]: 1.6-3.2), had higher prevalence of low waist-to-hip ratio (≤0.95/≤0.80 in men/women: aPRs 1.8 [95% CI:1.2-2.7]) and more daily smoking (aPR 1.7; 95% CI: 1.2-2.5). There were no differences in the proportions of patients with and without a family history of diabetes across subgroups (aPR 0.9; 95% CI: 0.7-1.1). Crude PRs for the demographic and clinical characteristics are reported in Supplementary Table 1 and showed essentially the same results as reported for the aPRs.

Biochemical characteristics of patients with PPDM and T2D are reported in Table 2 and the corresponding aPRs are shown in Figure 2B. Compared to patients with T2D, PPDM patients had lower plasma amylase levels (<17 U/L: aPRs 2.2; 95%CI: 1.1-4.3) and tended to have worse glycemic control (HbA1c ≥8.0%: aPRs 1.4; 95% CI: 0.8-2.4). Crude PRs for the biochemical characteristics are reported in Supplementary Table 2 and showed essentially the same results as reported for the aPRs.

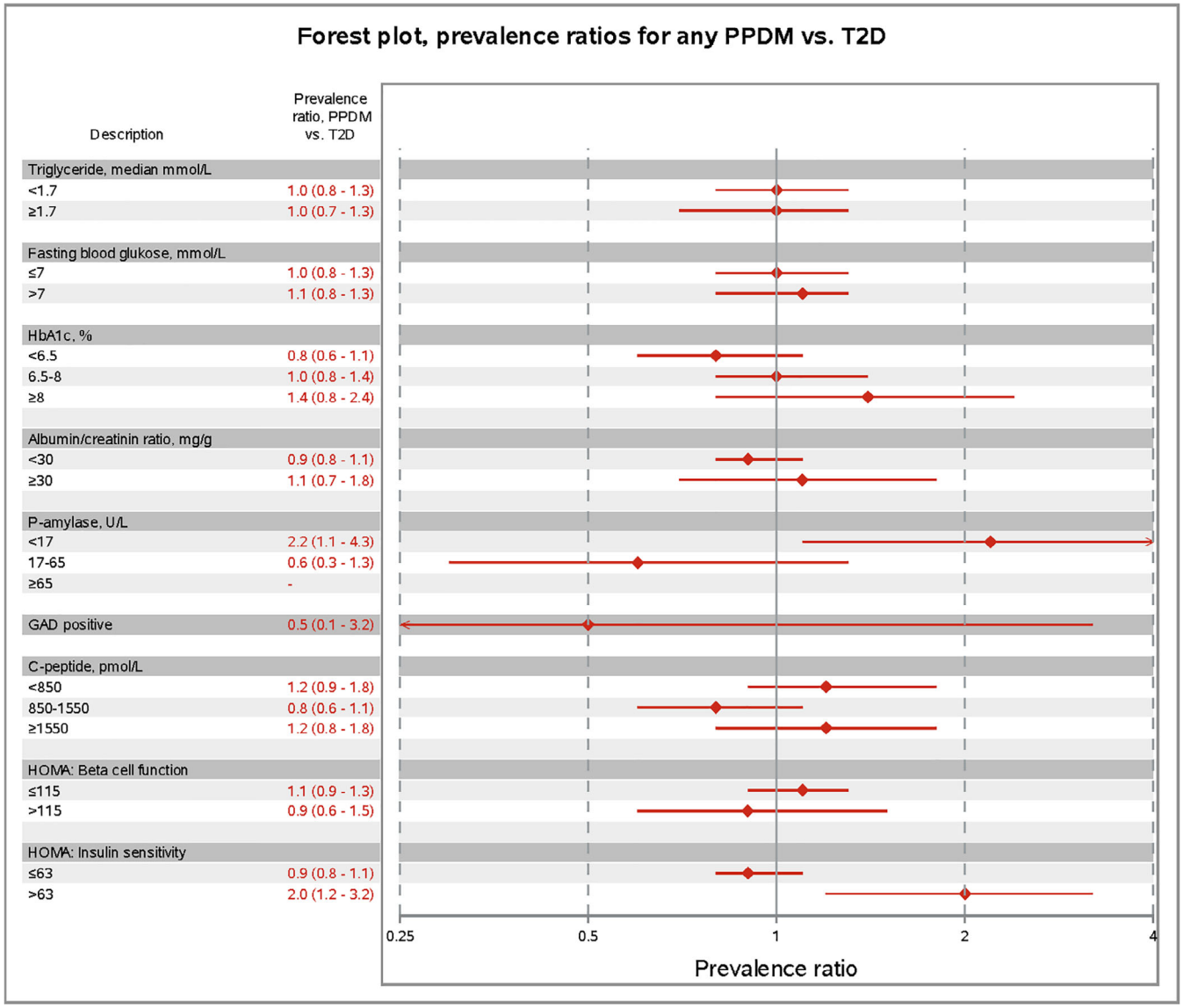

FIGURE 2 (Continued)

TABLE 2 Biochemical characteristics of patients with WHO-defined type 2 diabetes (T2D) and postpancreatitis diabetes mellitus (PPDM)

	All (n = 5564)	T2D (n = 5486)	PPDM (n = 78)
Median triglyceride, mmol/L (IQR)	1.6 (1.2; 2.3)	1.6 (1.2; 2.3)	1.6 (1.1; 2.3)
Triglyceride category, n (%)			
<1.7 mmol/L	2279 (41.0)	2246 (40.9)	33 (42.3)
≥1.7 mmol/L	2224 (40.0)	2194 (40.0)	30 (38.5)
Missing	1061 (19.1)	1046 (19.1)	15 (19.2)
Median fasting blood glucose, mmol/L (IQR)	7.1 (6.4; 8.2)	7.1 (6.4; 8.2)	7.3 (6.1; 8.8)
Fasting blood glucose category, n (%)			
≤7 mmol/L	2089 (37.5)	2060 (37.6)	29 (37.2)
>7 mmol/L	2486 (44.7)	2449 (44.6)	37 (47.4)
Missing	989 (17.8)	977 (17.8)	12 (15.4)
Median HbA1c, mmol/L (IQR)	6.6 (6.1;7.2)	6.5 (6.1;7.2)	6.8 (6.2;7.7)
HbA1c category, n (%)			
<6.5 mmol/L	2101 (37.8)	2078 (37.9)	23 (29.5)
6.5-8 mmol/L	2038 (36.6)	2009 (36.6)	29 (37.2)
>8 mmol/L	588 (10.6)	576 (10.5)	12 (15.4)
Missing	837 (15.0)	823 (15.0)	14 (17.9)
Median albumin creatinine ratio (IQR)	9.0 (4.0; 22.0)	9.0 (4.0; 22.0)	10.3 (4.0; 29.6)
Albumin creatinine ratio category, n (%)			
<30	3420 (61.5)	3376 (61.5)	44 (56.4)
≥30	891 (16.0)	877 (16.0)	14 (17.9)
Missing	1253 (22.5)	1233 (22.5)	20 (25.6)
Median P-amylase, U/L (IQR)	23.0 (16.0; 30.0)	23.0 (16.0; 30.0)	15.0 (11.0; 27.0)
P-amylase category, n (%)			
<17 U/L	266 (4.8)	258 (4.7)	8 (10.3)
17-65 U/L	699 (12.6)	693 (12.6)	6 (7.7)
>65 U/L	31 (0.6)	31 (0.6)	0 (0.0)
Missing	4568 (82.1)	4504 (82.1)	64 (82.1)
Median GAD, IU/L (IQR)	0.0 (0.0;0.0)	0.0 (0.0;0.0)	0.0 (0.0;0.0)
GAD positive (>25 IU/L), n (%)	164 (2.9)	163 (3.0)	<5
Median C-peptide, pmol/L (IQR)	1110.0 (831.8; 1477.0)	1110.0 (833.8; 1476.0)	1166.0 (675.1; 1638.0)
C-peptide category, n (%)			
<850 pmol/L	1276 (22.9)	1254 (22.9)	22 (28.2)
850-1550 pmol/L	2479 (44.6)	2451 (44.7)	28 (35.9)
>1550 pmol/L	1015 (18.2)	998 (18.2)	17 (21.8)
Missing	794 (14.3)	783 (14.3)	11 (14.1)
Median HOMA: beta cell function, (IQR)	90.9 (68.7; 117.8)	91.0 (68.9; 117.8)	82.9 (51.1; 114.5)
HOMA: Beta cell function category, n (%)			
≤115	3348 (60.2)	3298 (60.1)	50 (64.1)
>115	1227 (22.1)	1211 (22.1)	16 (20.5)
Missing	989 (17.8)	977 (17.8)	12 (15.4)
Median HOMA: Insulin sensitivity (IQR)	36.1 (26.8; 49.1)	36.2 (26.9; 49.0)	32.3 (23.4; 59.1)

TABLE 2 (Continued)

	All (n = 5564)	T2D (n = 5486)	PPDM (n = 78)
HOMA: Insulin sensitivity category, n (%)			
≤63	4065 (73.1)	4013 (73.1)	52 (66.7)
>63	510 (9.2)	496 (9.0)	14 (17.9)
Missing	989 (17.8)	977 (17.8)	12 (15.4)

Abbreviations: GAD, glutamic acid decarboxylase; HOMA, homeostatic assessment model; IQR, interquartile range; WHO, World Health Organization.

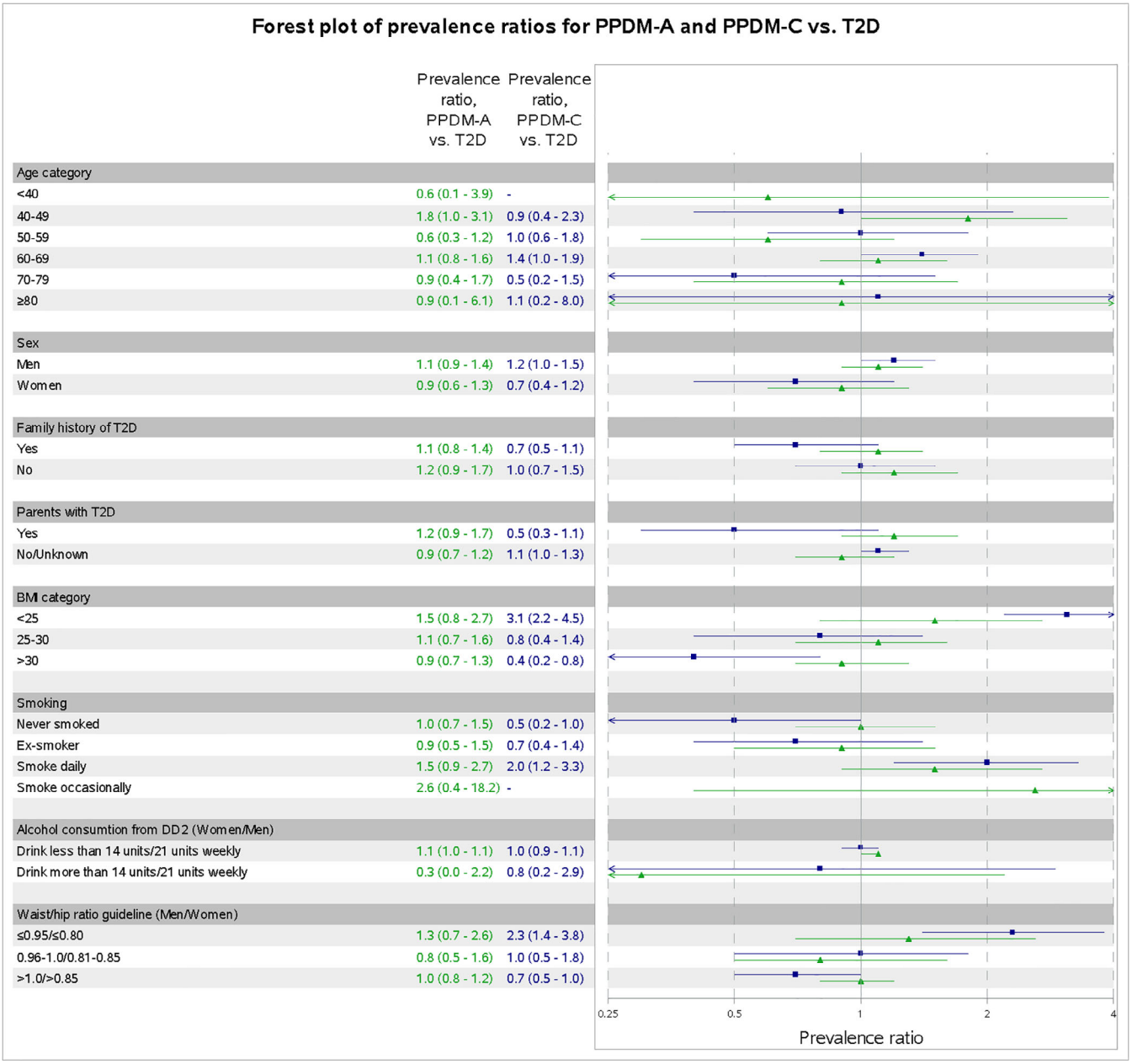

FIGURE 3 A, Age- and sex-adjusted prevalence ratios of demographic and clinical parameters for PPDM acute/chronic subtypes (PPDM-A and PPDM-C) vsT2D. B, Age- and sex-adjusted prevalence ratios of biochemical parameters for PPDM acute/chronic subtypes (PPDM-A and PPDM-C) vsT2D. Abbreviations: BMI, body mass index; DD2, Danish Centre for Strategic Research in Type 2 Diabetes; GAD, glutamic acid decarboxylase; HOMA, homeostatic assessment model; PPDM-A, postpancreatitis diabetes mellitus following acute-acutepancreatitis; PPDM-C, postpancreatitis diabetes mellitus asssocaited with-chronic pancreatitis; T2D, type 2 diabetes

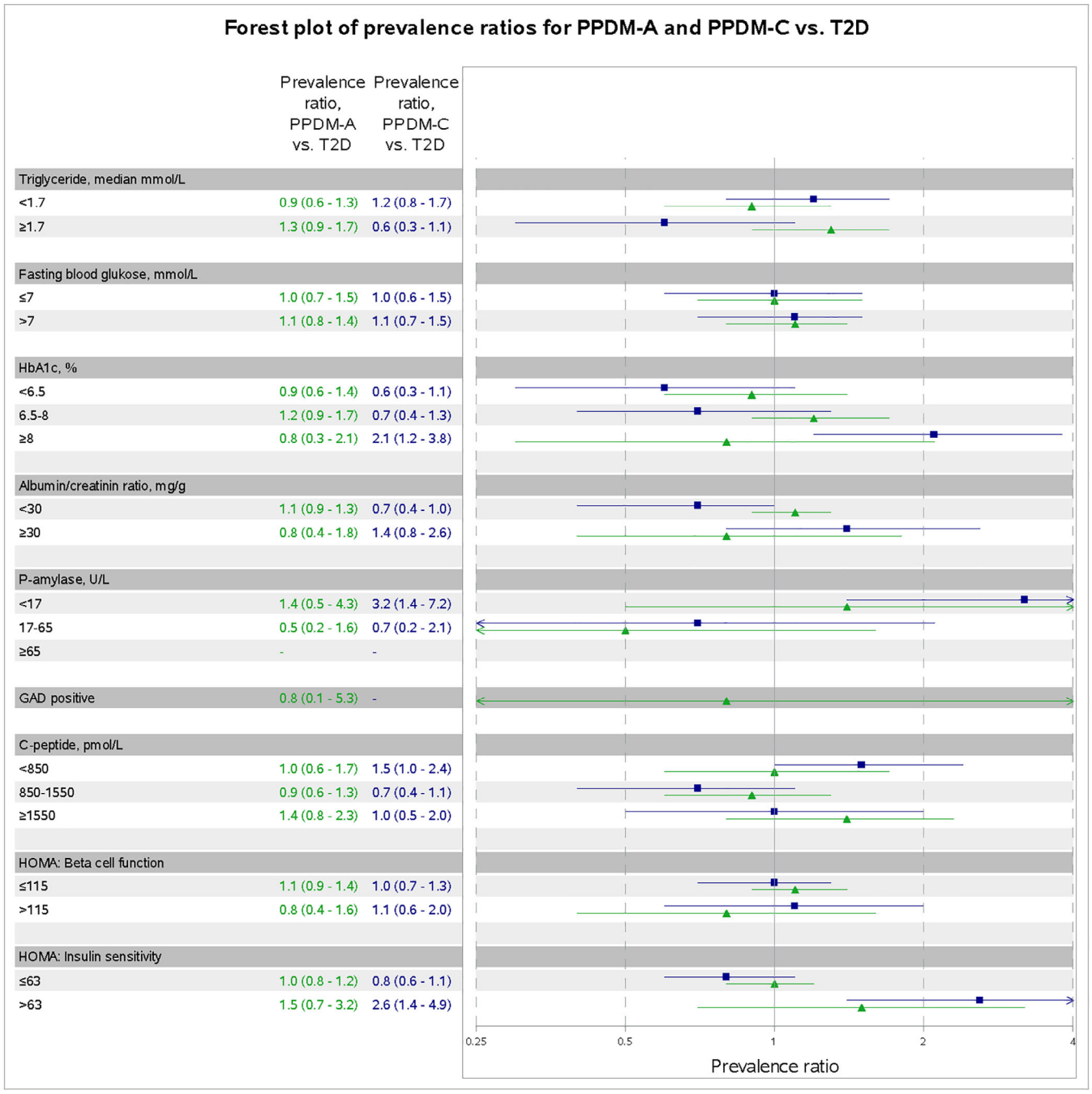

FIGURE 3 (Continued)

3.2 | Characteristics of PPDM-A vs T2D

Clinical and biochemical characteristics of patients with PPDM-A and T2D are reported in Supplementary Tables 1 and 2 and the corresponding aPRs are shown in Figure 3A,B. Compared to patients with T2D, PPDM-A patients tended to be more often normal or underweight (BMI ≤25.0 kg/m^2: aPR 1.5; 95% CI: 0.8-2.7) and daily smokers (aPRs 1.5; 95% CI: 0.9-2.7). Otherwise, PPDM-A patients were largely comparable to patients with T2D for the remaining parameters.

3.3 | Characteristics of PPDM-C vs T2D

Characteristics of patients with PPDM-C and T2D are reported in Supplementary Tables 1 and 2 and the corresponding aPRs are shown in Figure 3A,B. Patients

with PPDM-C had a more clearly increased prevalence of normal or underweight (BMI ≤25.0 kg/m^2: aPR 3.1; 95% CI: 2.2-4.5) and daily smoking (aPRs 2.0; 95% CI: 1.2-3.3) vs T2D, than was the case for PPDM-A patients. PPDM-C patients also had a clearly higher prevalence of low waist-to-hip ratio (≤0.95/≤0.80 in men/women: aPR 2.3; 95% CI: 1.4-3.8) and low plasma amylase levels (<17 U/L: aPRs 3.2; 95% CI: 1.4-7.2) compared to T2D patients. Likewise, patients with PPDM-C had impaired insulin secretion (C-peptide <850 pmol/L: aPR 1.5; 95% CI: 1.0-2.4) and worse glycaemic control (HbA1c ≥8.0%: aPRs 2.1; 95%CI: 1.2-3.8) compared to T2D.

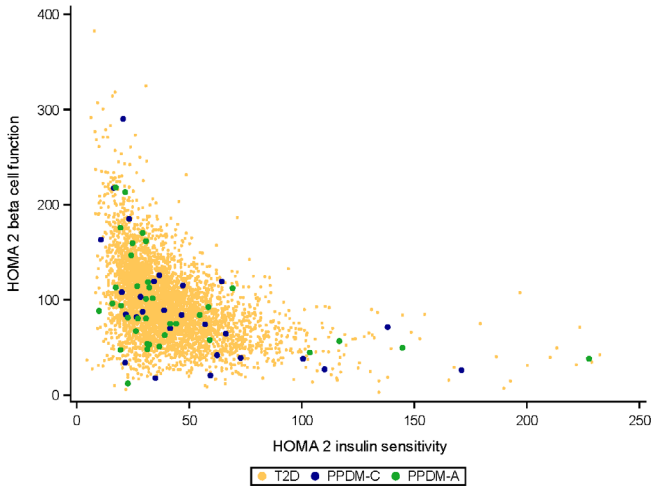

FIGURE 4 Plot of insulin sensitivity and beta cell function of patients with T2D and PPDM acute/chronic subtypes (PPDM-A and PPDM-C). Abbreviations: HOMA, homeostatic assessment model; PPDM-A, postpancreatitis diabetes mellitus-acute; PPDM-C, postpancreatitis diabetes mellitus-chronic; T2D, type 2 diabetes

3.4 | Glucose metabolism in PPDM vs T2D

Measures of glucose metabolism as determined by the HOMA2 model are presented in Table 2 and the corresponding aPRs are shown in Figures 2B and 3B. Compared to patients with T2D, PPDM patients had higher insulin sensitivity (HOMA2S >63: aPR 2.0; 95%CI: 1.2-3.2). This difference was primarily confined to patients with PPDM-C (HOMA2S >63: aPR 2.6; 95% CI: 1.4-4.9), whereas no differences in insulin sensitivity was observed for patients with PPDM-A compared to T2D. Also, following adjustment for waist-to-hip ratio, insulin sensitivity was higher in patients with PPDM compared to T2D (HOMA2S >63: aPR 1.7; 95% CI: 1.1-2.6). There were no differences between diabetes subgroups in relation to beta-cell function as determined by the HOMA2 model.

A plot of HOMA2S (insulin sensitivity) and HOMA2B (beta cell function) of the two PPDM cohorts and patients with T2D are shown in Figure 4. Overall, the cohorts showed overlapping measures of insulin sensitivity and beta cell function and no clearly defined subphenotypes were evident.

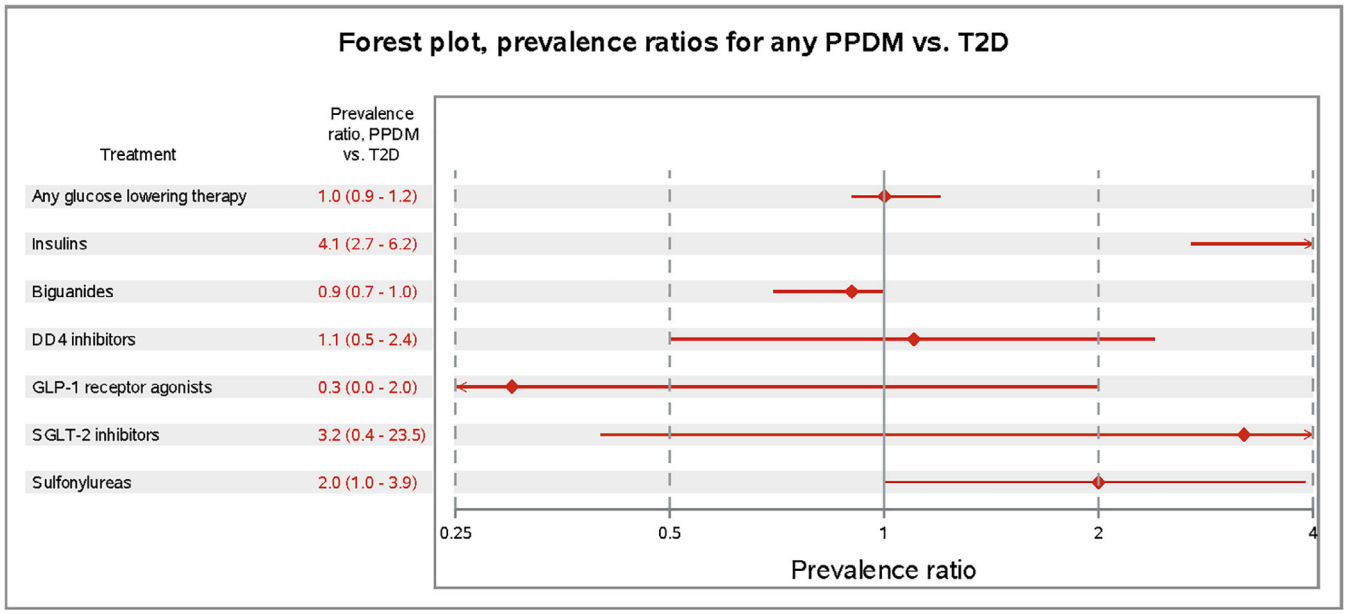

FIGURE 5 Age- and sex-adjusted prevalence ratios of prescription patterns of antidiabetic medications for PPDM vs T2D. Abbreviations: DPP4, dipeptidyl peptidase 4 inhibitors; GLP-1, glucagon-like peptide-1; PPDM, postpancreatitis diabetes mellitus; SGLT-2, sodium-glucose cotransporter-2; T2D, type 2 diabetes

3.5 | Glucose lowering therapies

Information on prescription patterns of glucose lowering therapies is reported in Table 1. Compared to T2D, PPDM patients were more often prescribed insulins (aPR 4.1; 95% CI: 2.7-6.2) and sulfonylureas (aPR 2.0; 95% CI: 1.0-3.9) but less often biguanides (aPR 0.9; 95% CI: 0.7-1.0) (Figure 5). Crude PRs are reported in Table 1 and showed essentially the same results as reported for the aPRs.

Prescription patterns of glucose lowering therapies were largely comparable across PPDM acute/chronic subtypes (Supplementary Figure 1 and Supplementary Table 1).

4 | DISCUSSION

We investigated the prevalence and characteristics of PPDM in a cohort of patients with new or recent onset diabetes diagnosed in an everyday clinical care setting. Among 5564 patients with clinically diagnosed T2D, the proportion of patients with PPDM was 1.4%. Compared to patients with T2D, the overall PPDM cohort was characterized by lower BMI, less central obesity, higher smoking prevalence, and lower plasma amylase levels. Parameters of glucose metabolism were largely indistinguishable for patients with PPDM-A vs T2D, whereas patients with PPDM-C vs T2D had a more clear pattern of increased insulin sensitivity, impaired insulin secretion, and worse glycemic control.

4.1 | Prevalence of PPDM

The proportion of patients with PPDM of 1.4% in our cohort is close to prevalence estimates obtained from other population-based studies. Accordingly, Woodmansey and coworkers reported that the proportion of "pancreatogenic diabetes" was 1.8% among 31 789 newly diagnosed adult-onset diabetes patients from the primary care setting in the United Kingdom.[6] However, they also included patients with pancreatic cancer, hemochromatosis, cystic fibrosis, and previous pancreatic surgery, which may explain the slightly higher proportion of pancreatogenic diabetes observed. Comparable incidence estimates were observed in another population-based study from New Zealand.[26] Based on these studies it has been projected that diabetes following diseases of the exocrine pancreas constitutes approximately 1.6% of all patients with new-onset diabetes in adults.[5] In the same report it was estimated that PPDM comprises the majority of these cases (80%) and is most frequently observed after acute pancreatitis, which is also in line with the findings from our study.[5]

4.2 | Clinical characteristics and glucose metabolism in PPDM vs T2D

Patients with PPDM had lower BMI and lower waist-to-hip ratio when compared to T2D. These findings are in keeping with previous observations and most likely reflect that many patients with PPDM have concomitant exocrine pancreatic insufficiency resulting in maldigestion and decreased nutrient absorption.[27] This is further supported by the finding that PPDM patients had lower plasma amylase levels, which has been associated with pancreatic exocrine insufficiency.[25]

We did not observe any clear separation of PPDM from T2D in relation to parameters of glucose metabolism when plotting HOMA parameters for individual subjects. Also, in the group-based analysis patients with PPDM-A were largely indistinguishable from T2D. In contrast, patients with PPDM-C were characterized by low C-peptide levels (indicative of decreased insulin secretion) and increased insulin sensitivity. This may imply that different pathophysiological mechanisms are involved in PPDM subtypes, although findings must be interpreted with caution because of the limited number of patients in the PPDM subgroups. The low C-peptide levels and increased insulin sensitivity observed in PPDM-C patients corresponds to the classic pancreatogenic diabetes that stems from islet-cell destruction induced by the fibroinflammatory process underling chronic pancreatitis.[15,16] Taken together with impaired secretion of pancreatic counterregulatory hormones (eg, glucagon and somatostatin) and decreased nutrient absorption, these observations may explain the increased risk of hypoglycemia observed in these patients.[8]

The frequency of patients with a family history of diabetes was proportionate between individuals with PPDM and T2D. This suggest that genetic predisposition may not only be a common finding in T2D but also in PPDM. Comparable findings were observed in a US-based study where the proportion of chronic pancreatitis patients with a family history of diabetes was higher among patients with diabetes compared to patients without diabetes.[15] Likewise, a study based on genetic risk profiling of common genetic variants associated with beta-cell dysfunction showed that genetic risk scores were comparable between chronic pancreatitis patients and individuals with T2D.[14] Taken together with the overlapping parameters of glucose metabolism between patients with PPDM and T2D seen in the present study, these findings imply that PPDM is a heterogenous condition sharing overlapping features with T2D. From the current available data it is therefore not clear whether PPDM should be considered a separate diabetes subtype or a special form

of T2D arising when pancreatic endocrine dysfunction is accelerated by pancreatic disease in genetically predisposed individuals.[28]

4.3 | Glucose lowering therapies in PPDM vs T2D

Prescription patterns of glucose lowering therapies revealed that patients with PPDM were more often prescribed insulins and sulfonylureas compared to individuals with T2D. This indicates that patients with PPDM have more severe hyperglycemia as also indicated by HbA1c levels. However, sulfonylureas should generally be avoided in PPDM and insulins should be titrated with caution because of the excess risk of hypoglycemia associated with this condition.[11] This is particularly important in patients with PPDM-C, as these patients seem to have increased insulin sensitivity and thus may be more prone to develop hypoglycemia following exposure to insulin and/or sulfonylureas. Also, most experts recommend that biguanides are prescribed in PPDM as these have been associated with a survival benefit in this context.[7] Notwithstanding this recommendation, we observed that patients with PPDM less frequently received a biguanide prescription compared to individuals with T2D.

4.4 | Autoimmunity in PPDM vs T2D

A recent case series primarily including children and adolescent patients with acute pancreatitis suggested that attacks of pancreatitis may increase risk for autoimmune mediated diabetes (type 1 diabetes).[17] The proposed mechanism included posttranslational protein modifications of β-cell antigens and neoepitope generation induced by pancreatic inflammation, which could potentially initiate events for loss of β-cell self-tolerance (ie, autoimmunity).[17] To test this hypothesis, we investigated the proportion of GAD-antibody positivity between diabetes subgroups but did not find support for autoimmunity as a prominent characteristic of PPDM or its acute/chronic subtypes. Our findings are in keeping with a recent prospective cohort study where only one out of 152 patients with acute pancreatitis developed GAD-antibody positivity during a two-year follow-up period.[29] Taken together, these observations do not support that loss of β-cell self-tolerance is a common mechanism in adult patients with PPDM.

4.5 | Study strengths and limitations

A strength of our study is the large prospectively maintained cohort of recent onset diabetes patients in routine care, with detailed phenotyping of all patients including various biochemical assessment parameters.[18] This allowed for a comprehensive characterization of patients with exclusion of other rare types of diabetes that could potentially blur the observed findings.[22] Likewise, exact linkage with Danish health registers enabled a complete identification of all patients in the cohort who had a past history of acute or chronic pancreatitis.[20]

Our study also has some limitations. Most important, the cross-sectional study design precludes any causal inference of the observed associations. Hence, it is not possible to dissert if development of PPDM preceded or followed some of the clinical and biochemical characteristics that we examined. Also, the absolute number of patients with PPDM was relatively low even in our large cohort, and complete data were not available for all the studied parameters, leading to limited statistical precision for some associations. Finally, although our PPDM definition was based on a previously published algorithm,[5] some patients classified as PPDM may have had classical T2D related to its high prevalence.

4.6 | Conclusions

The proportion of patients with PPDM among those with recent clinically diagnosed T2D is ~1.5% in an everyday clinical care setting. Compared to T2D, patients with PPDM are characterized by more often normal or low BMI and a lower prevalence of central obesity, as well as lower plasma amylase and C-peptide levels. Parameters of glucose metabolism are largely indistinguishable for patients with PPDM-A and T2D, whereas PPDM-C patients seem to have decreased insulin secretion but increased insulin sensitivity. This may indicate different underlying pathophysiological mechanisms and have implications for treatment.

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CONFLICT OF INTERESTS

No conflicts of interest relevant to this article were reported from any of the authors. The funding source had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

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