This is the peer reviewed version of the following article: Comparing diabetes due to diseases of the exocrine pancreas to type 1 and type 2 diabetes using propensity score matching, which has been published in final form at

<https://doi.org/10.1016/j.pan.2020.05.023> by Lanzinger S et al.

© 2020. This manuscript version is made available under the CC-BY-NC-ND 4.0 license

<http://creativecommons.org/licenses/by-nc-nd/4.0/>

Comparing diabetes due to diseases of the exocrine pancreas to type 1 and type 2 diabetes using propensity score matching

Short title: Diabetes due to diseases of the exocrine pancreas

Stefanie Lanzinger^{1,2}, Wolfram Karges³, Sigrun Merger⁴, Markus Laimer⁵, Ursula Lück⁶, Christian Wagner⁷, Karsten Milek⁸, Reinhard W. Holl^{1,2} for the DPV

Initiative

¹Institute of Epidemiology and Medical Biometry, ZIBMT, University of Ulm, Ulm, Germany

²German Center for Diabetes Research (DZD), München-Neuherberg, Germany

³Division of Endocrinology and Diabetes, Medical Faculty, RWTH Aachen University, German Center for Diabetes Research (DZD), Aachen, Germany.

⁴Medical Clinic IV, Clinic for Endocrinology, Diabetology, Metabolism, and Nutrition Medicine, Clinic Coburg, Coburg, Germany

⁵Department of Endocrinology, Diabetology and Clinical Nutrition, University Hospital Bern, Switzerland

⁶Department for Children and Adolescent Medicine, State Hospital Baden-Mödling, Austria

⁷Specialized Diabetes Practice, Saaldorf-Surheim, Germany

⁸Specialized Diabetes Practice, Hohenmölsen, Germany

Corresponding Author:

Stefanie Lanzinger, PhD

Institute of Epidemiology and Medical Biometry, ZIBMT, University of Ulm

Albert-Einstein-Allee 41

89081 Ulm, Germany

Telephone: 0731 50-25483

Fax: 0731 50-25309

Email: stefanie.lanzinger@uni-ulm.de

Abstract

Objective: To estimate the prevalence of diabetes due to diseases of the exocrine pancreas (DEP) using data of the multicentre diabetes patient follow-up registry. Moreover, we aimed at comparing individuals with diabetes due to DEP to individuals with type 1 and type 2 diabetes.

Methods: Individuals with DEP, type 1 or type 2 diabetes ≥ 18 years of age were studied. We aggregated the most recent treatment year per patient and used propensity scores to match diabetes due to DEP to type 1 and type 2 diabetes. Matching was conducted one-to-one with sex, age, diabetes duration, migration background and the German index of socioeconomic deprivation as covariates.

Results: We identified 7,093 (1.6%) individuals with diabetes due to DEP. In the matched cohort DEP-type 1 diabetes we observed a similar daily insulin dose (0.62 IU/kg (95% confidence interval: 0.60-0.63), 0.60 IU/kg (0.58-0.62)) and significant differences regarding microvascular (41.0% (39.7-42.2), 45.3% (44.0-46.6)), and macrovascular disease (16.6% (15.7-17.6), 14.7% (13.8-15.6)). HbA1c (8.2% (8.1-8.3), 7.9% (7.8-8.0)), daily insulin dose (0.60 IU/kg (0.58-0.62), 0.56 IU/kg (0.54-0.58)) and event rates of severe hypoglycemia (23.9 events/100 PY (21.4-26.8), (9.5 events/100 PY (8.0-11.2)) were significantly higher in individuals with diabetes due to DEP compared to type 2 diabetes.

Conclusions: Using registry data, rare diabetes types such as diabetes due to DEP can be studied with a significant sample size. Our study identified differences and similarities between adult individuals with DEP related diabetes and type 1 or type 2 diabetes.

Keywords: diabetes due to diseases of the exocrine pancreas; type 1 diabetes; type 2 diabetes; propensity score matching

Introduction

Epidemiological studies on diabetes due to diseases of the exocrine pancreas (DEP) are rare so far (1). The prevalence of diabetes due to DEP was estimated to range from 5-10% in Western populations with diabetes (2). Ewald and colleagues (3) studied the largest sample size on this form of secondary diabetes so far. The authors examined 1,868 individuals with diabetes, which were admitted to a German hospital. The prevalence of diabetes due to DEP was 9.2% (n=172) in this study (3). Vujasinovic et al (4) studied a small cohort of 150 patients with type 1 and type 2 diabetes in Slovenia and found that exocrine pancreatic insufficiency was present in 5.4%. Recently a study conducted in England showed that DEP related diabetes is the second most type of new onset diabetes in adults (5). Moreover, a population-based study in New Zealand reported an increasing prevalence of diabetes due to DEP from 2006 to 2014 (0.01 to 0.03% in the general population) (6). Reasons for an increasing trend might be more frequent pancreatic surgery, prolonged survival of patients with cystic fibrosis and an increasing prevalence of chronic pancreatitis (7).

Diabetes due to DEP results from exocrine as well as endocrine pancreas damage and affects all hormone-producing cells in the islet (8). This diabetes form is heterogeneous due to different underlying diseases (8, 9). Chronic pancreatitis and pancreatic cancer are the main reasons for DEP related diabetes in adult individuals (3, 9, 10). Other forms are diabetes after pancreatic surgery, hemochromatosis or cystic fibrosis (8). Previously, the distribution of causes of diabetes due to DEP was reported to be 79% chronic pancreatitis, 8% pancreatic cancer (ductal adenocarcinoma), 7% hemochromatosis, 4% cystic fibrosis and 2% pancreatic surgery (3). So far, there are no specific guidelines on treatment of patients with DEP related diabetes (9, 10). However, metformin or insulin therapy were mentioned as the first-line therapy in a review of Hart and colleagues (9).

Whereas, glucagon-like peptide-1 (GLP-1) analogues and inhibitors of dipeptidyl peptidase 4 (DPP-4) are not recommended (8, 9). Individuals with diabetes due to DEP might be at high risk for severe hypoglycemia due to an impaired insulin as well as glucagon secretion (8, 11). However, evidence from epidemiological studies is rare (8). Cui and Anderson (2) reported that microvascular complications might be similar between DEP related diabetes and type 1 diabetes. Moreover, Hart et al emphasized that more data are needed in order to show robust results on microvascular and macrovascular disease in diabetes due to DEP (9).

The objective of our study was to investigate the prevalence of diabetes due to DEP in adult patients using data of the comprehensive, multicenter diabetes patient follow-up registry (DPV). Moreover, we compared clinical characteristics of DEP related diabetes with adult patients with type 1 and type 2 diabetes.

Methods

Study population

Patients included in the study were identified from the multicenter, prospective DPV registry. As of March 2018, the DPV documentation software was used by 471 hospitals and diabetes specialized practices in Germany (425 centers), Austria (42 centers), Switzerland (3 centers) and in Luxemburg (1 center). Twice a year, anonymized data are collected locally at Ulm University, where data are further validated and analyzed. Data collection for quality control and diabetes research was approved by the ethics committee of Ulm University and by local review boards of the participating centers. The DPV initiative was described in more detail elsewhere (12, 13).

Individuals with diabetes due to DEP, type 1 or type 2 diabetes ≥ 18 years of age, which were documented in the DPV database between January 2000 and March 2018 were included in the study. Characteristics of pediatric individuals with diabetes due to DEP from the DPV registry were published previously (14), therefore, we focused on adult individuals only, due to the clear etiologic differences between both groups. Data of the most recent treatment year was aggregated (median) for the analyses. HbA_{1c} values were standardized to the Diabetes Control and Complications Trial (DCCT) reference range of 4.05–6.05% (20.7–42.6 mmol/mol) using the multiple of the mean transformation method to account for different laboratory methods (15). Severe hypoglycemia was defined as an event associated with severe cognitive impairment, including seizure, convulsion or loss of consciousness (severe hypoglycemic coma) (16). Diabetic ketoacidosis (DKA) was defined as venous pH < 7.3 or bicarbonate < 15 mmol/L (17). History of microalbuminuria, diabetic retinopathy and peripheral neuropathy were defined as microvascular disease. Myocardial infarction, peripheral artery disease and stroke were combined as macrovascular disease. Individuals with a median systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg or individuals with antihypertensive treatment were specified as hypertensive. Moreover, dyslipidemia was defined as total cholesterol ≥ 200 mg/dl, LDL-cholesterol ≥ 160 mg/dl, HDL-cholesterol < 40 mg/dl, triglyceride ≥ 150 mg/dl or receiving lipid lowering treatment.

We used the German index of socioeconomic deprivation (GISD) as a proxy for the individual socioeconomic status (18). The GISD represents regional deprivation based on indicators of education, occupation and income and was linked to patients via the 5-digit postcodes of patient's residency. The GISD was divided into quintiles from low to

high regional deprivation. Migration background was defined as at least one parent not born in Germany, Austria, Luxemburg or Switzerland.

Diagnosis of diabetes due to DEP was gathered from respective ICD-10 codes or from the free text field area of DPV. We searched free text fields of the DPV software for terms associated with diabetes due to DEP with a focus on the five main causes: 1) chronic pancreatitis/pancreas insufficiency, 2) pancreatic cancer, 3) pancreatic surgery, 4) hemochromatosis and 5) cystic fibrosis (9). The majority of individuals (88%) with diabetes due to DEP were diagnosed at first documentation in the DPV registry, whereas, 12% were registered as type 1 or type 2 diabetes first and changed do diabetes due to DEP during follow-up.

Statistical analyses

Results of descriptive analyses are presented as mean (standard deviation) for continuous variables and proportions for categorical variables.

We used the propensity score method (greedy-matching algorithm) in order to balance covariates between patients with DEP related diabetes and patients with type 1 diabetes or type 2 diabetes (19, 20). Sequential matching was performed, in a first step individuals with diabetes due to DEP were matched one-to-one to individuals with type 1 diabetes. In a second step, patients with diabetes due to DEP were matched to patients with type 2 diabetes. We used logistic regression models to estimate propensity scores for DEP related diabetes vs. type 1 diabetes and for DEP related diabetes vs. type 2 diabetes. Sex, age, diabetes duration, migration background and GISD were included as covariates. Age, diabetes duration and GISD were included into the model continuously as well as categorized (age <50 years, 50-<60 years, 60-<70 years, 70-<80 years, ≥80 years; diabetes duration ≤5 years, >5-15 years, >15 years; GISD quintiles).

Standardized differences were calculated for the unmatched and matched cohorts in order to determine whether the propensity score models has been adequately specified (19). A standardized difference less than 0.1 indicates an adequately specified model.

As outcomes, we focused on body-mass-index (BMI), daily insulin dose, HbA1c, event rates of severe hypoglycemia, hypoglycemic coma and DKA, frequency of microvascular and macrovascular disease, frequency of hypertension and dyslipidemia. Specific microvascular complications (microalbuminuria, diabetic retinopathy and peripheral neuropathy) were studied as secondary outcomes. Linear, logistic and negative binomial regression were conducted to compare outcomes between the matched cohorts.

Statistical analyses were conducted using SAS version 9.4 (SAS Institute Inc, Cary,NC). A two-sided p-value <0.05 was considered as statistically significant.

Results

Between January 2000 and March 2018, 435,511 patients ≥18 years of age were documented in DPV. About 14.6% (n=63,551) type 1 diabetes, 78.5% (n=341,656) type 2 diabetes, 1.6% (n=7,093) with diabetes due to DEP and 5.3% (23,211) with other diabetes types. Chronic pancreatitis/pancreas insufficiency was the main cause of diabetes due to DEP (n=4,153, 58.5%) followed by pancreatic cancer (n=971, 13.7%) and pancreatic surgery (n=872, 12.3%) (Table 1). We identified 601 (8.5%) patients with cystic fibrosis-related diabetes of the exocrine pancreas and 496 (7.0%) with diabetes due to hemochromatosis. Age at diabetes onset ranged from 21 years (cystic fibrosis) to 63 years (pancreatic cancer). A small proportion of patients were treated with GLP-1 analogues or DPP-4 inhibitors, although incretin-based therapy is not recommended in patients with diabetes due to DEP. Proportion of patients treated with

oral anti-diabetic medication (OAD) only, insulin only, a combination of OAD and insulin or lifestyle therapy only are shown in [Figure 1](#). The majority of patients received a treatment with insulin only, ranging from 66.1% in patients with pancreatic cancer to 74.4% in patients with previous pancreatic surgery.

HbA1c was highest in the pancreatitis group (8.5%) and lowest in the cystic fibrosis group (7.2%) (Table 1). We observed high event rates of severe hypoglycemia and hypoglycemic coma in all subgroups. Individuals with previous pancreatic surgery showed highest hypoglycemia event rates (30.6 events of severe hypoglycemia/100 PY (95%-confidence interval: 29.3-32.0), 11.9 events of hypoglycemic coma/100 PY (11.1-12.8)), lowest rates were found in patients with cystic fibrosis (7.8 events of severe hypoglycemia/100 PY (7.1-8.7), 2.8 events of hypoglycemic coma/100 PY (2.4-3.3)). Frequency of microvascular disease ranged from 8.3% to 45.4%, frequency of macrovascular disease from 1.8% to 18.9% (cystic fibrosis to pancreatitis). Dyslipidemia was common in all subgroups ranging from 64.8% in cystic fibrosis to 77.9% in pancreatic cancer.

Comparison of diabetes due to DEP to type 1 diabetes and type 2 diabetes

Table 2 represents a description of the entire and matched cohort for comparing patients with diabetes due to DEP and type 1 diabetes. We identified 5,962 matched pairs of diabetes due to DEP and type 1 diabetes. A comparison of individuals with diabetes due to DEP and type 2 diabetes is shown in table 3. For the individuals with diabetes due to DEP 6,655 type 2 diabetes matching partners were found.

In the matched cohort of diabetes due to DEP and type 1 diabetes, BMI was significantly lower in DEP related diabetes (23.9 kg/m² (95%-CI: 23.8-24.0)) compared to type 1

diabetes (26.0 kg/m² (25.9-26.1), Table 4). Daily insulin dose in DEP did not differ significantly from type 1 diabetes. HbA1c was significantly lower in DEP (8.2% (8.1-8.3)) compared to type 1 diabetes (8.5% (8.4-8.6)). We observed higher event rates of severe hypoglycemia, hypoglycemic coma and DKA in individuals with diabetes due to DEP in contrast to individuals with type 1 diabetes. Proportion of patients with microvascular disease was lower in DEP related diabetes (41.0% (39.7-42.2)) than in type 1 diabetes (45.3% (44.0-46.6)). However, frequency of microalbuminuria was higher in DEP (11.2% (10.5-12.1) compared to type 1 diabetes (8.9% (8.2-9.7), p<0.001), but both retinopathy (3.4% (2.9-3.9) vs 6.4% (5.8-7.1), p<0.001) and peripheral neuropathy (32.5% (31.3-33.7) vs 36.6% (35.4-37.9), p<0.001) were lower in DEP.

Macrovascular disease were more frequent in diabetes due to DEP (16.6% (15.7-17.6)) compared to type 1 diabetes (14.7 (13.8-15.6)). The proportion of patients with hypertension was higher in diabetes due to DEP (56.8% (55.5-58.1) compared to type 1 diabetes (53.7% (52.3-55.0)). But, we observed no statistically significant difference in dyslipidemia between matched pairs of DEP and type 1 diabetes.

Results of the matched cohort of diabetes due to DEP and type 2 diabetes showed a significantly lower BMI (24.0 kg/m² (23.8-24.1)) in DEP in contrast to type 2 diabetes (32.2 kg/m² (32.1-32.4), Table 4). Daily insulin dose as well as HbA1c was higher in individuals with diabetes due to DEP (0.60 IU/kg (0.58-0.62), 8.2% (8.1-8.3)) compared to individuals with type 2 diabetes (0.56 IU/kg (0.54-0.58), 7.9% (7.8-8.0)). Events of severe hypoglycemia, hypoglycemic coma and DKA were more frequent in diabetes due to DEP. Frequency of microvascular disease (microalbuminuria 10.9% (10.2-11.7) vs 13.2% (12.5-14.1), p<0.001; retinopathy 3.2% (2.8-3.6%) vs 4.1% (3.6-4.6), p=0.007; peripheral neuropathy 32.0% (30.9-33.1) vs 32.3% (31.2-33.4), p=0.683) and macrovascular disease were lower in diabetes due to DEP than in type 2 diabetes.

Hypertension and dyslipidemia were less frequent in individuals with diabetes due to DEP compared to individuals with type 2 diabetes.

Discussion

Results from the DPV registry showed similar insulin requirement between individuals with diabetes due to DEP and type 1 diabetes. Moreover, event rates of severe hypoglycemia and hypoglycemic coma were significantly higher in DEP compared to type 1 diabetes. HbA1c and frequency of microvascular disease were significantly lower in individuals with diabetes due to DEP in contrast to type 1 diabetes. Whereas, macrovascular disease were more frequent in DEP related diabetes compared to type 1 diabetes. Daily insulin dose, HbA1c, event rates of severe hypoglycemia and hypoglycemic coma were significantly higher in individuals with DEP compared to individuals with type 2 diabetes. Proportion of patients with microvascular and macrovascular disease were higher in type 2 diabetes than in DEP.

Few epidemiological studies on DEP have been conducted so far and individuals with DEP are often misclassified as type 2 diabetes (1, 3, 5). The prevalence of diabetes due to DEP (1.6%) was lower compared to previous estimates (5-10%) (2, 3). However, DEP patients might be treated in specialized clinics and therefore might be overrepresented in single-center reports, or underrepresented in the multicenter DPV-registry.

Consistent to previous reports from Germany and New Zealand, the most common reason for diabetes due to DEP was chronic pancreatitis followed by pancreatic cancer in our study (3, 6). This may explain the unexpectedly high insulin requirement, as both chronic inflammation and tumor cachexia are accompanied by insulin resistance. Most

of the patients with diabetes due to DEP were treated with insulin only (66.1% to 74.4%). However, a small proportion of patients were treated with GLP-1 analogues or DPP-4 inhibitors, although several studies do not recommend incretin-based therapy in patients with DEP (8). GLP-1 analogues and DPP-4 inhibitors might be associated with an increased risk of pancreatitis and pancreatic cancer and therefore should be avoided as treatment for patients with diabetes due to DEP (21). A recent population-based study observed a protective effect of metformin on mortality risk in individuals with postpancreatitis related diabetes (10). Therefore, the authors recommend metformin as first-line therapy in this patient group. However, Cho and colleagues (10) also emphasized that further investigations are necessary in order to suggest optimal treatment for other subgroups of DEP related diabetes. Wynne et al (8) suggested initiating insulin therapy in patients with diabetes due to DEP with a dose calculation similar to patients with type 1 diabetes. The authors support our findings of similar daily insulin requirement in individuals with diabetes due to DEP (0.62 IU/kg (0.60-0.63)) and type 1 diabetes 0.60 IU/kg (0.58-0.62)). In accordance to previous studies, we observed high event rates of severe hypoglycemia in DEP (8, 11, 22). Factors contributing to the high event rate of severe hypoglycemia are an enzyme substitution therapy due to the exocrine pancreas insufficiency and the glucagon deficiency in DEP (11). With regard to the high event rates of severe hypoglycemia, individuals with diabetes due to DEP might benefit from the use of insulin pumps and continuous glucose monitoring systems nowadays available. Clinical trials have shown a reduction in hypoglycemia, especially in type 1 diabetes, in association with glucose monitoring systems (23). Proper use of diabetes technology is important and therefore, diabetes education in DEP should be comparable to type 1 and type 2 diabetes.

Individuals with type 2 diabetes showed a low event rate of severe hypoglycemia in our study, possibly due to the less frequently usage of insulin therapy.

A review of Cui and Anderson (2011) reported that patients with DEP related diabetes might have the same incidence of retinal and renal disease as patients with type 1 diabetes. Results of our matched cohort showed lower proportion of patients with microvascular disease in DEP (41.0% (39.7-42.2)) than in type 1 diabetes (45.3% (44.0-46.6)). However, the proportion of microvascular disease in general was higher compared to proportions reported in the literature review by Hart et al (9) (diabetic retinopathy 37%, diabetic nephropathy 29% in patients with diabetes of the exocrine pancreas). Heterogeneity of diabetes duration (often undiagnosed) in different forms of DEP-diabetes have to be taken into account. Given the high frequency of microvascular disease in DEP, results of our study indicate that guidelines on screening and treatment of microvascular complications in diabetes due to DEP should be similar to type 1 and type 2 diabetes. Current guidelines of the American Diabetes Association recommend annual assessment of urine albumin and estimated glomerular filtration rate in adults with type 1 diabetes (diabetes duration ≥ 5 years) and type 2 diabetes (24). Moreover, current guidelines suggest screening for diabetic retinopathy every 1-2 years and annually for peripheral neuropathy (24).

We found a higher frequency of macrovascular disease in diabetes due to DEP (16.6% (15.7-17.6)) compared to type 1 diabetes (14.7 (13.8-15.6)). A previous DPV study investigated the frequency of vascular risk factors in adult patients with cystic fibrosis related diabetes and type 1 diabetes (25). Hypertension was more common in type 1 diabetes compared to cystic fibrosis related diabetes in that study (25).

We observed significantly higher HbA1c values in diabetes due to DEP (8.2% (8.1-8.3)) compared to type 2 diabetes 7.9% (7.8-8.0)). Worse glycemic control in the former group was also reported in a study from England (5). Moreover, the authors found a markedly greater insulin requirement in individuals with DEP when comparing to individuals with type 2 diabetes (5). In accordance to the study from England, our results also showed higher daily insulin dose (0.60 IU/kg (0.58-0.62)) in DEP compared to type 2 diabetes (0.56 IU/kg (0.54-0.58)).

One limitation of our study is the fact that we could not adjust for lifestyle, individual social factors and dietary habits as these factors are challenging to consistently document in registries. However, we considered the GISD as a proxy for individual socioeconomic status. Further, we identified 7,093 individuals with diabetes of the exocrine pancreas by combining both ICD-10-diagnostic codes and searching free text fields of the DPV software. We cannot exclude that this might have resulted in an underestimated number of individuals with diabetes due to DEP.

The novelty of our study is that we used registry data in order to study a rare diabetes type with a significant sample size. In contrast to our study, previous analyses on DEP related diabetes usually had a quite small sample size. Moreover, we used the concept of propensity score matching as an alternative method to traditional regression analysis. Using standardized differences it is simple to check whether the model has been adequately specified (19).

Diabetes due to DEP is rare and epidemiological studies using a significant sample size are missing so far. Using data of the DPV registry, we identified 7,093 adult patients with diabetes due to DEP. Therefore, our results can serve as a basis to reconsider treatment options for individuals with rare diabetes types such as DEP related diabetes. Overall,

results of this study showed that diabetes care in individuals with diabetes due to DEP should be intensified. Previous studies have shown that DEP is often misclassified as type 2 diabetes (3, 5), however, results of our study show that treatment and diabetes education for this rare diabetes type might be similar to that of type 1 and type 2 diabetes. Individuals with diabetes due to DEP might benefit from the use of insulin pumps and continuous glucose monitoring systems. Screening guidelines for microvascular complications should be similar to type 1 and type 2 diabetes. Due to the limited access of gastroenterologists to modern diabetes treatment modalities, interdisciplinary collaboration between diabetologists and gastroenterologist is very important.

Acknowledgements

The authors thank all participating centers of the DPV initiative, especially the collaborating centers in this investigation. Special thanks to Andreas Hungele and Ramona Ranz for support and the development of the DPV documentation software and Katharina Fink and Esther Bollow for the DPV data management (clinical data managers, Ulm University).

Funding

The study was funded by the German Diabetes Association (DDG). Additional support was provided by the Federal Ministry of Education and Research within the German Competence Network Diabetes Mellitus, which was integrated into the German Center for Diabetes Research (DZD, grant 82DZD0017G) as of January 2015.

Conflict of interest

The authors declare that there is no duality of interest associated with this manuscript.

References

1. Petrov MS. Diabetes of the exocrine pancreas: American diabetes association-compliant lexicon. *Pancreatology* 2017;17(4):523-526
2. Cui Y, Andersen DK. Pancreatogenic diabetes: Special considerations for management. *Pancreatology* 2011;11(3):279-294
3. Ewald N, Kaufmann C, Raspe A, Kloer HU, Bretzel RG, Hardt PD. Prevalence of diabetes mellitus secondary to pancreatic diseases (type 3c). *Diabetes Metab Res Rev* 2012 May;28(4):338-342
4. Vujasinovic M, Zaletel J, Tepes B, Popic B, Makuc J, Lenart ME, Predikaka M, Rudolf S. Low prevalence of exocrine pancreatic insufficiency in patients with diabetes mellitus. *Pancreatology* 2013;13(4):343-346
5. Woodmansey C, McGovern AP, McCullough KA, Whyte MB, Munro NM, Correa AC, Gatenby PAC, Jones SA, de Lusignan S. Incidence, demographics, and clinical characteristics of diabetes of the exocrine pancreas (type 3c): A retrospective cohort study. *Diabetes Care* 2017 Nov;40(11):1486-1493
6. Pendharkar SA, Mathew J, Petrov MS. Age-and sex-specific prevalence of diabetes associated with diseases of the exocrine pancreas: A population-based study. *Digestive and Liver Disease* 2017;49(5):540-544
7. Ewald N, Bretzel RG. Diabetes mellitus secondary to pancreatic diseases (type 3c)--are we neglecting an important disease?. *Eur J Intern Med* 2013 Apr;24(3):203-206

8. Wynne K, Devereaux B, Dornhorst A. Diabetes of the exocrine pancreas. J Gastroenterol Hepatol 2019;34(2):346-354
9. Hart PA, Bellin MD, Andersen DK, Bradley D, Cruz-Monserrate Z, Forsmark CE, Goodarzi MO, Habtezion A, Korc M, Kudva YC. Type 3c (pancreatogenic) diabetes mellitus secondary to chronic pancreatitis and pancreatic cancer. The Lancet Gastroenterology & Hepatology 2016;1(3):226-237
10. Cho J, Scragg R, Pandol SJ, Goodarzi MO, Petrov MS. Antidiabetic medications and mortality risk in individuals with pancreatic cancer-related diabetes and postpancreatitis diabetes: A nationwide cohort study. Diabetes Care 2019 Jun 21
11. Czako L, Hegyi P, Rakonczay Z,Jr, Wittmann T, Otsuki M. Interactions between the endocrine and exocrine pancreas and their clinical relevance. Pancreatology 2009;9(4):351-359
12. Bohn B, Karges B, Vogel C, Otto K, Marg W, Hofer SE, Fröhlich-Reiterer E, Holder M, Plamper M, Wabitsch M. 20 years of pediatric benchmarking in germany and austria: Age-dependent analysis of longitudinal follow-up in 63,967 children and adolescents with type 1 diabetes. PloS One 2016;11(8):e0160971
13. Hofer SE, Schwandt A, Holl RW, Austrian/German DPV Initiative. Standardized documentation in pediatric diabetology: Experience from austria and germany. J Diabetes Sci Technol 2016 Aug 22;10(5):1042-1049
14. Lanzinger S, Welters A, Thon A, Konrad K, Kapellen T, Grulich-Henn J, Raddatz D, Holl RW. Comparing clinical characteristics of pediatric patients with pancreatic diabetes

to patients with type 1 diabetes: A matched case-control study. Pediatric Diabetes 2019;20(7):955-963

15. Rosenbauer J, Dost A, Karges B, Hungele A, Stahl A, Bachle C, Gerstl EM, Kastendieck C, Hofer SE, Holl RW, DPV Initiative and the German BMBF Competence Network Diabetes Mellitus. Improved metabolic control in children and adolescents with type 1 diabetes: A trend analysis using prospective multicenter data from germany and austria. Diabetes Care 2012 Jan;35(1):80-86
16. Abraham MB, Jones TW, Naranjo D, Karges B, Oduwole A, Tauschmann M, Maahs DM. Assessment and management of hypoglycemia in children and adolescents with diabetes. Pediatric Diabetes 2018
17. Wolfsdorf JJ, Allgrove J, Craig ME, Edge J, Glaser N, Jain V, Lee WW, Mungai LN, Rosenbloom AL, Sperling MA, Hanas R, International Society for Pediatric and Adolescent Diabetes. ISPAD clinical practice consensus guidelines 2014. diabetic ketoacidosis and hyperglycemic hyperosmolar state. Pediatr Diabetes 2014 Sep;15 Suppl 20:154-179
18. Kroll LE, Schumann M, Hoebel J, Lampert T. Regionale unterschiede in der Gesundheit–Entwicklung eines sozioökonomischen deprivationsindex für deutschland 2017
19. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. Multivariate Behav Res 2011 May;46(3):399-424

20. Parsons L. Reducing bias in a propensity score matched-pair sample using greedy matching techniques. In *Proceedings of the twenty-sixth annual SAS users group international conference 2001*, SAS Institute Inc.
21. Rickels MR, Bellin M, Toledo FG, Robertson RP, Andersen DK, Chari ST, Brand R, Frulloni L, Anderson MA, Whitcomb DC, PancreasFest Recommendation Conference Participants. Detection, evaluation and treatment of diabetes mellitus in chronic pancreatitis: Recommendations from PancreasFest 2012. *Pancreatology* 2013;13(4):336-342
22. Stoop TF, Ateeb Z, Ghorbani P, Scholten L, Arnelo U, Besselink MG, Del Chiaro M. Impact of endocrine and exocrine insufficiency on quality of life after total pancreatectomy. *Annals of Surgical Oncology* 2019:1-10
23. American Diabetes Association. 7. diabetes technology: Standards of medical care in Diabetes—2020. *Diabetes Care* 2020;43(Supplement 1):S77-S88
24. American Diabetes Association. 11. microvascular complications and foot care: Standards of medical care in diabetes– 2020. *Diabetes Care* 2020;43(Supplement 1):S135-S151
25. Konrad K, Scheuing N, Badenhoop K, Borkenstein MH, Gohlke B, Schöfl C, Seufert J, Thon A, Holl RW. Cystic fibrosis-related diabetes compared with type 1 and type 2 diabetes in adults. *Diabetes Metab Res* 2013;29(7):568-575

Figure Legends

Figure 1. Treatment of individuals with diabetes due to diseases of the exocrine pancreas stratified by subgroup.

Table 1. Characteristics of adult patients with diabetes due to diseases of the exocrine pancreas (n = 7,093), stratified by subgroup.

	Subgroups of diseases of the exocrine pancreas				
	Chronic pancreatitis/pancreas insufficiency	Pancreatic cancer	Previous pancreatic surgery	Cystic fibrosis	Hemochromatosis
	n = 4,153	n = 971	n = 872	n = 601	n = 496
	mean (SD)	mean (SD)	mean (SD)	mean (SD)	mean (SD)
Age (years)	55.4 (12.2)	67.4 (11.0)	64.5 (13.5)	26.7 (10.1)	58.4 (15.0)
Age at diabetes onset (years)	47.7 (12.7)	63.0 (12.8)	55.2 (15.8)	21.1 (9.6)	50.5 (16.4)
Diabetes duration (years)	7.7 (8.6)	4.4 (7.3)	9.2 (10.7)	5.6 (5.4)	7.9 (8.8)
BMI (kg/m ²)	24.1 (5.1)	24.2 (4.6)	24.5 (5.3)	20.2 (3.5)	24.8 (5.2)
HbA1c (mmol/mol)	69.1 (27.9)	61.7 (23.3)	62.0 (24.4)	55.7 (20.7)	62.8 (25.0)
HbA1c (%)	8.5 (2.6)	7.8 (2.1)	7.8 (2.2)	7.2 (1.9)	7.9 (2.3)
Daily insulin dose (IU/kg)	0.6 (0.9)	0.5 (0.5)	0.5 (0.3)	0.7 (0.5)	0.6 (0.4)
SMBG	2.8 (1.8)	2.8 (1.7)	3.0 (1.7)	3.5 (1.7)	2.8 (1.7)

	percent	percent	percent	percent	percent
Male sex	79.5	52.2	62.2	43.1	68.8
Migration background	1.3	1.2	1.4	5.7	3.8
CT (1-3 injections/day)	34.8	46.5	36.8	35.7	39.9
ICT (4-8 injections/day)	63.8	52.3	60.1	55.0	58.8
Insulin pump	1.4	1.2	3.0	9.3	1.3
Continuous glucose monitoring systems	8.4	6.4	7.0	3.8	5.0
OAD	15.2	17.3	14.0	8.7	21.6
Biguanides	9.4	10.0	8.9	1.0	13.7
Alpha-glucosidase inhibitor	0.6	0.5	0.3	0.0	1.2
Sulfonylureas	3.1	4.0	3.9	2.5	3.4
Glinides	1.8	2.2	0.9	5.5	2.4
Thiazolidindione	0.2	0.2	0.2	0.0	0.6
DPP-4 inhibitors	3.7	6.0	4.1	0.2	7.5
GLP-1 analogues	0.2	0.2	0.2	0.0	1.4

SGLT-2 inhibitors	1.1	1.8	1.3	0.0	0.8
Microvascular disease	45.4	28.3	41.6	8.3	42.9
Macrovascular disease	18.9	12.7	16.2	1.8	17.3
Hypertension	57.9	64.4	61.4	21.8	60.3
Dyslipidemia	76.2	77.9	74.4	64.8	77.0
	event rates (95%-CI)	event rates (95%-CI)	event rates (95%-CI)	event rates (95%-CI)	event rates (95%-CI)
Hospital admissions per 1 PY	1.3 (1.2; 1.3)	1.8 (1.8; 1.9)	1.2 (1.2; 1.3)	0.7 (0.7; 0.8)	1.1 (1.1; 1.2)
Severe hypoglycaemia per 100 PYs	20.3 (19.8; 20.8)	21.7 (20.5; 23.0)	30.6 (29.3; 32.0)	7.8 (7.1; 8.7)	15.2 (14.0; 16.5)
Hypoglycaemic coma per 100 PYs	8.7 (8.3; 9.0)	9.3 (8.5; 10.2)	11.9 (11.1; 12.8)	2.8 (2.4; 3.3)	6.4 (5.6; 7.3)
DKA per 100 PYs	9.6 (9.3; 10.0)	6.8 (6.2; 7.6)	5.7 (5.1; 6.3)	0.5 (0.3; 0.8)	6.2 (5.4; 7.0)

Table 2. Description of covariates of the entire and matched study cohort for type 1 diabetes versus diseases of the exocrine pancreas.

	Entire study cohort			Matched study cohort		
	Type 1 diabetes	Diseases of the exocrine pancreas	Standardized difference	Type 1 diabetes	Diseases of the exocrine pancreas	Standardized difference
	n = 63,551	n = 7,093		n = 5,962	n = 5,962	
	mean (SD) or %	mean (SD) or %		mean (SD) or %	mean (SD) or %	
Age (years)	39.0 (19.3)	55.9 (15.8)	0.961	55.2 (15.9)	54.9 (15.4)	-0.018
<50 years	69.8	32.9	-0.795	35.1	35.5	0.008
50-<60 years	13.0	26.1	0.335	27.4	27.1	-0.007
60-<70 years	8.7	20.4	0.337	19.1	19.4	0.007
70-<80 years	6.4	15.8	0.303	14.1	13.7	-0.011
≥80 years	2.2	4.9	0.150	4.3	4.3	0.002
Diabetes duration (years)	15.4 (13.3)	7.3 (8.6)	-0.719	8.0 (8.9)	8.0 (8.9)	-0.002
≤5 years	23.3	53.0	0.643	48.8	48.8	0.001

>5-15 years	36.9	30.9	-0.128	32.7	33.1	0.007
>15 years	39.8	16.1	-0.547	18.5	18.1	-0.010
Male sex	53.5	69.8	0.340	67.4	68.4	0.022
Migration background	4.8	1.9	-0.165	1.5	1.8	0.022
GISD	3.0 (1.5)	3.3 (1.4)	0.187	3.2 (1.5)	3.2 (1.5)	0.022
20% least deprived	21.7	15.5	-0.159	18.1	16.8	-0.033
21-40%	20.6	20.2	-0.009	20.5	20.9	0.011
41-60%	17.4	12.7	-0.131	13.8	13.4	-0.012
61-80%	16.8	24.6	0.194	20.6	21.9	0.032
20% most deprived	23.5	26.9	0.078	27.0	27.0	-0.002

Table 3. Description of covariates of the entire and matched study cohort for type 2 diabetes versus diseases of the exocrine pancreas

	Entire study cohort			Matched study cohort		
	Type 2 diabetes	Diseases of the exocrine pancreas	Standardized difference	Type 2 diabetes	Diseases of the exocrine pancreas	Standardized difference
	n = 341,656	n = 7,093		n = 6,655	n = 6,655	
	mean (SD) or %	mean (SD) or %		mean (SD) or %	mean (SD) or %	
Age (years)	68.6 (12.9)	55.9 (15.8)	-0.877	56.5 (15.2)	56.5 (15.3)	-0.001
<50 years	8.8	32.9	0.621	32.0	31.7	-0.007
50-<60 years	15.3	26.1	0.267	27.2	26.5	-0.016
60-<70 years	24.8	20.4	-0.105	19.7	21.0	0.033
70-<80 years	31.8	15.8	-0.383	15.5	15.8	0.008
≥80 years	19.3	4.9	-0.453	5.6	5.0	-0.025
Diabetes duration (years)	10.2 (9.2)	7.3 (8.6)	-0.326	7.4 (8.4)	7.3 (8.6)	-0.010
≤5 years	35.1	53.0	0.366	53.0	52.7	-0.007

>5-15 years	39.8	30.9	-0.187	30.8	31.0	0.006
>15 years	25.1	16.1	-0.224	16.2	16.3	0.002
Male sex	52.6	69.8	0.358	69.2	69.7	0.012
Migration background	1.5	1.9	0.026	1.8	1.7	-0.006
GISD	3.2 (1.5)	3.3 (1.4)	0.026	3.2 (1.4)	3.3 (1.4)	0.015
20% least deprived	16.1	15.5	-0.017	15.5	15.6	0.003
21-40%	21.0	20.2	-0.020	21.1	20.2	-0.022
41-60%	16.4	12.7	-0.105	12.6	12.8	0.004
61-80%	16.1	24.6	0.213	24.7	24.4	-0.007
20% most deprived	30.3	26.9	-0.075	26.1	27.0	0.021

Table 4. Comparison of outcomes between matched pairs of type 1 diabetes and diabetes due to diseases of the exocrine pancreas and between matched pairs of type 2 diabetes and diabetes due to diseases of the exocrine pancreas (least square means with 95%-confidence intervals estimated from linear, logistic and negative binomial regression models).

Outcome	Adjusted mean estimates (95%-confidence interval)					
	Type 1 diabetes	Diseases of the exocrine pancreas	p-value	Type 2 diabetes	Diseases of the exocrine pancreas	p-value
	n = 5,962	n = 5,962		n = 6,655	n = 6,655	
BMI (kg/m ²)	26.0 (25.9-26.1)	23.9 (23.8-24.0)	<0.001	32.2 (32.1-32.4)	24.0 (23.8-24.1)	<0.001
Daily insulin dose (IU/kg)	0.60 (0.58-0.62)	0.62 (0.60-0.63)	0.249	0.56 (0.54-0.58)	0.60 (0.58-0.62)	0.010
HbA1c (%)	8.5 (8.4-8.6)	8.2 (8.1-8.3)	<0.001	7.9 (7.8-8.0)	8.2 (8.1-8.3)	<0.001
Severe hypoglycemia/100 PY	17.8 (16.0-19.9)	20.8 (18.7-23.2)	0.044	9.5 (8.0-11.2)	23.9 (21.4-26.8)	<0.001
Hypoglycemic coma/100 PY	5.4 (4.7-6.3)	8.5 (7.5-9.6)	<0.001	3.4 (2.8-4.2)	9.8 (8.8-11.0)	<0.001
DKA/100 PY	6.3 (5.6, 7.1)	7.8 (7.1, 8.7)	0.006	0.3 (0.2-0.4)	8.0 (7.2-8.8)	<0.001
Microvascular disease (%)	45.3 (44.0-46.6)	41.0 (39.7-42.2)	<0.001	43.7 (42.5-44.9)	40.4 (39.2-41.6)	<0.001
Macrovascular disease (%)	14.7 (13.8-15.6)	16.6 (15.7-17.6)	0.003	19.0 (18.0-19.9)	16.6 (15.7-17.5)	<0.001

Hypertension (%)	56.8 (55.5-58.1)	53.7 (52.3-55.0)	<0.001	70.8 (69.7-72.0)	58.1 (56.8-59.3)	<0.001
Dyslipidemia (%)	76.2 (74.9, 77.5)	75.4 (74.1-76.7)	0.3879	90.2 (89.3-91.0)	75.9 (74.6-77.1)	<0.001

Figure 1