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Risk of pancreatic cancer in people with new-onset diabetes: A Danish nationwide population-based cohort study

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ABSTRACT

Background: New onset diabetes (NOD) in people 50 years or older may indicate underlying pancreatic ductal adenocarcinoma (PDAC). The cumulative incidence of PDAC among people with NOD remains uncertain on a population-based level.
Methods: This was a nationwide population-based retrospective cohort study based on the Danish national health registries. We investigated the 3-year cumulative incidence of PDAC in people 50 years or older with NOD. We further characterised people with pancreatic cancer-related diabetes (PCRD) in relation to demographic and clinical characteristics, including trajectories of routine biochemical parameters, using people with type 2 diabetes (T2D) as a comparator group.
Results: During a 21-year observation period, we identified 353,970 people with NOD. Among them, 2105 people were subsequently diagnosed with pancreatic cancer within 3 years (0.59%, 95% CI [0.57–0.62%]). People with PCRD were older than people with T2D at diabetes diagnosis (median age 70.9 vs. 66.0 years ($P < 0.001$) and had a higher burden of comorbidities ($P = 0.007$) and more prescriptions of medications used to treat cardiovascular diseases (all $P < 0.001$). Distinct trajectories of HbA1c and plasma triglycerides were observed in PCRD vs. T2D, with group differences observed for up to three years prior to NOD diagnosis for HbA1c and up to two years for plasma triglyceride levels.
Conclusions: The 3-year cumulative incidence of PDAC is approximately 0.6% among people 50 years or older with NOD in a nationwide population-based setting. Compared to T2D, people with PCRD are characterised by distinct demographic and clinical profiles, including distinctive trajectories of plasma HbA1c and triglyceride levels.

1. Introduction

Pancreatic ductal adenocarcinoma (PDAC) continues to be a leading cause of cancer-related death worldwide [1]. Most patients (80–85%) are diagnosed at an advanced stage where surgical resection, the only curative treatment, is no longer possible [2]. The treatment possibilities for this patient group are reduced to palliative treatment and best supportive care. In general, treatment advancements have been limited for this patient group. In contrast, the treatment options and prognosis for patients with resectable pancreatic cancer (15–20%) continue to improve with the increasing availability of multimodality neoadjuvant therapy, more aggressive surgical approaches, and potent adjuvant regimens [1]. This underlines the importance of diagnosing patients at early disease stages.

Population-based screening for PDAC is unrealistic due to its low incidence in the general population [1,3]. Therefore, the focus has been directed toward subgroups of individuals with a higher-than-average risk of PDAC that may benefit from surveillance. Patients with pancreatic cancer-related germline mutations, a history of familiar pancreatic cancer, and mucinous cystic pancreatic lesions have been identified as target populations amendable to

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surveillance [3,4]. In addition, new-onset diabetes (NOD) in individuals above 50 years has received attention in this context [3,4]. In a population-based study from Olmsted County in the United States, 0.85% of people with NOD older than 50 years were subsequently diagnosed with PDAC within 3 years of meeting glycaemic criteria for diabetes [5]. This corresponds to a six-to eight-fold increased risk of pancreatic cancer compared to the general population. These findings were subsequently confirmed in an independent cohort from the same geographical region. In contrast, studies based on health insurance databases found considerably lower estimates (3-year cumulative incidence 0.3%) which may question the relevance of NOD as a target population for early detection of PDAC [6,7].

The Danish national health registries are among the largest in the world and provide a unique opportunity to investigate the association between NOD and PDAC on a larger scale than in previous studies [8]. In addition to information on diagnosis codes, the registers hold information on various data that can be linked using unique personal identification numbers [9]. Of particular interest, data on prescriptions of glucose-lowering medications can be combined with data on diagnosis codes [10]. This is important as the prescription of glucose-lowering medications has been recommended as first-line therapy (in addition to lifestyle changes) for type 2 diabetes (T2D) since 2005 [11]. Hence, the combination of information on diagnosis codes and prescription of glucose-lowering medications can be used to identify people with NOD (and subsequently PDAC) on a population-based level with high accuracy [8]. In addition, the Danish health registries hold information on biochemical variables routinely used in everyday clinical practice [12]. These data may be used to identify distinctive patterns of biochemical parameters that can differentiate patients with pancreatic cancer-related diabetes (PCRD) from other diabetes subtypes, including the much more prevalent T2D [13].

In a population-based nationwide setting, the aim of this study was to investigate the 3-year cumulative incidence of PDAC among people diagnosed with NOD at age 50 years or older. In addition, we aimed to characterise the demographic, clinical, and biochemical characteristics of people with PCRD vs. T2D.

2. Methods

2.1. Study design and data sources

This was a retrospective nationwide cohort study of people diagnosed with NOD in Denmark from the 1st of January 1998 to the 31st of December 2018. We used data from the Danish National Patient Registry, the Danish National Prescription Registry, and the Civil Registration System for the primary analysis. In addition, we extracted data from the Income Statistics Register and the Danish Education Register for baseline characteristics. All registries were linked individually using unique identification numbers assigned to all Danish residents at birth or immigration [9].

Diagnoses of NOD, pancreas cancer, and comorbidities were extracted from the Danish National Patient Registry. This is a nationwide register containing discharge diagnoses and corresponding dates from both outpatient and inpatient hospital contacts. Since 1994, Danish National Patient Registry data have been coded using the International Coding of Disease version 10 (ICD-10).

Information on medication prescriptions was extracted from the Danish National Prescription Registry, which covers all prescription medicines sold in Denmark since 1996. The registry contains data on the date of dispensing, product name, and product code based on the Anatomical Therapeutic Chemical (ATC) code [10].

Laboratory data were extracted from the National LABKA database, which collects data from Denmark's largest clinical biochemistry and clinical immunology laboratories [12].

2.2. Study cohort

People with diabetes were identified using a previously published algorithm based on either an ICD-10 diagnosis code of diabetes (E10-14.x, G63.2, H28.0, H36.0, M14.2, O24.x or R73.x) or an ATC code of glucose-lowering medication (A10.x.) [14–16]. We included ATC codes of glucose-lowering therapies in the definition of diabetes to capture patients with diabetes managed in the primary care setting without hospital contacts. The diabetes onset date was defined as the first occurrence of an ICD-10 or an ATC code. Patients diagnosed with diabetes before the 1st of January 1998 or under age 50 at NOD diagnosis were excluded. Thus, the final study cohort comprised of people with NOD diagnosed at age 50 or older during the study period.

2.3. Classification of PCRD and T2D

Among people with NOD, patients with pancreatic cancer were identified (ICD-10 codes: C25.x or Z850F). People diagnosed with PDAC before, on the same data as NOD diagnosis or three years after NOD diagnosis were excluded, and the remaining group was defined as PCRD. The threshold of three years for PCRD diagnosis was chosen based on recent pathophysiological investigations showing that glycaemic changes in the context of PDAC can be detected for up to three years before PDAC diagnosis [17]. In the group of people with NOD without pancreatic cancer, we classified people as having Type 1 diabetes if they had received at least one ICD-10 code of Type 1 diabetes mellitus (E10.x) and no ATC code of "blood glucose-lowering drugs except for insulins" (A10B.x). People with Type 1 diabetes were subsequently excluded, and the remaining people were pragmatically classified as T2D. This was done to focus our study on people with PCRD and T2D, as T2D is the most challenging diabetes subgroup to differentiate from PCRD in everyday clinical practice.

2.4. Demographic, clinical, and biochemical characteristics

Several baseline characteristics were established based on ICD-10 and ATC codes, and the specific codes and criteria are reported in Supplementary Table 1. The Charlson Comorbidity Index was calculated using a previously published algorithm [18] (Supplementary Table 2). Routine biochemical variables with plausible biological links to pancreatic cancer were extracted from the LABKA database at baseline and compared between diabetes subgroups. In addition, the four biochemical parameters with the most significant numerical difference at baseline were further investigated for their temporal profile before and after NOD diagnosis. Accordingly, median trajectories three years before and after NOD diagnosis were explored for plasma levels of HbA1c, triglycerides, alkaline phosphatase, and C-reactive protein.

2.5. Statistical analysis

Baseline data are presented as the number (%) of people, mean (standard deviation [SD]), or median (interquartile range [IQR]) as appropriate. The 3-year cumulative incidence of PDAC following NOD diagnosis was estimated and reported with a 95% confidence interval (CI). Two sensitivity analyses were done to test period and misclassification effects on PDAC cumulative incidence estimates. We compared demographics and clinical characteristics for people with PCRD vs. T2D using Student's t-tests or Mann-Whitney U tests for continuous variables and Chi-squared or Fisher's exact tests for

categorical variables. We used multivariable logistic regression to assess the variables independently associated with the presence of PCRD (vs. T2D). Trajectories of selected laboratory parameters were characterised based on the following procedures 1) calculation of the median laboratory value for each person and year before and after NOD diagnosis (in case of several values of the same laboratory type within the year), 2) moving each median to the nearest whole year time point, −3, −2, −1, 0, 1, 2, 3 where, e.g., −2 corresponds to the values from year −3 to −2 before NOD diagnosis, and 3) calculating the grand median of the given laboratory type for PCRD and T2D for each time point. The lower and upper interquartile were calculated in the same way. The trajectories of medians and upper and lower interquartile were graphically displayed. A Mann-Whitney *U* test for the difference in medians between PCRD and T2D was performed for each time point using a Bonferroni-corrected alpha level of 0.00714 corresponding to the alpha level of 0.05 divided by 7 (number of repeated tests). Data management and statistical analyses were performed using SAS (9.4) and STATA (17.0).

2.6. Ethics and data availability

Epidemiological studies in Denmark based on national health registries do not demand approval from an ethical committee. Statistics Denmark made anonymized data available (Project Identifier 708,466). Only research institutions authorised by The Danish Health Data Authority can apply for the data.

3. Results

The study base included 8,116,129 Danish citizens. After excluding people without diabetes, people with NOD diagnosed before January 1st, 1998, and people with NOD diagnosed before age 50, the final study cohort comprised 353,970 people with NOD (Fig. 1).

3.1. Cumulative 3-year PDAC incidence

Among the 353,970 people diagnosed with NOD, 2105 patients were subsequently diagnosed with PDAC within three years and were considered to have PCRD. This corresponds to a cumulative 3-year PDAC incidence of 0.59% (95% CI [0.57–0.62%]). The 3-year cumulative PDAC incidence estimates from sensitivity analyses are reported in Supplementary Table 3. In a cohort restricted to the first half of the study period (1998–2008), the cumulative 3-year PDAC incidence was 0.59% (95% CI [0.55–0.63%]). In a cohort restricted to the second half of the study period (2008–2018), the cumulative 3-year PDAC incidence was 0.60% (95% CI [0.56–0.63%]). In a restricted cohort excluding people receiving glucose-lowering therapies without a diabetes-related ICD-10 code, but with a diagnosis of obesity and/or polycystic ovarian syndrome, the 3-year cumulative PDAC risk was 0.60% (95% CI [0.57–0.62%]).

3.2. Demographic and clinical characteristics of PCRD vs. T2D

Table 1 reports the baseline demographic and clinical characteristics of people with PCRD vs. T2D. Compared to T2D, people with PCRD were older ($P < 0.001$) (Fig. 2), more likely to be women ($P < 0.001$), and at lower income strata ($P = 0.006$). In contrast, people with T2D had more comorbidities ($P = 0.007$). They also redeemed more prescriptions of concomitant medications, including antihypertensives, antithrombotics, statins, anxiolytics, and antidepressants, compared to people with PCRD ($P < 0.001$). Prescription of opioids was more prevalent in people with PCRD ($P < 0.001$). People with T2D had higher exposure to smoking and alcohol abuse ($P < 0.001$). Multivariate analysis confirmed the independence and significance of the associations for age, sex, comorbidities, and concomitant medications, except for antithrombotics and anxiolytics (Table 2).

3.3. Biochemical characteristics of PCRD vs. T2D

Table 3 reports the biochemical characteristics of people with PCRD vs. T2D at diabetes diagnosis. People with PCRD were characterised by higher plasma levels of HbA1c but lower levels of cholesterol (HDL) and triglycerides compared to people with T2D ($P < 0.001$). People with PCRD also had elevated levels of cholestatic liver function tests, lower plasma levels of haemoglobin and albumin, and increased C-reactive protein levels compared to people with T2D ($P < 0.001$).

Fig. 3 shows plasma level trajectories of HbA1c, triglyceride, alkaline phosphatase, and C-reactive protein three years before and

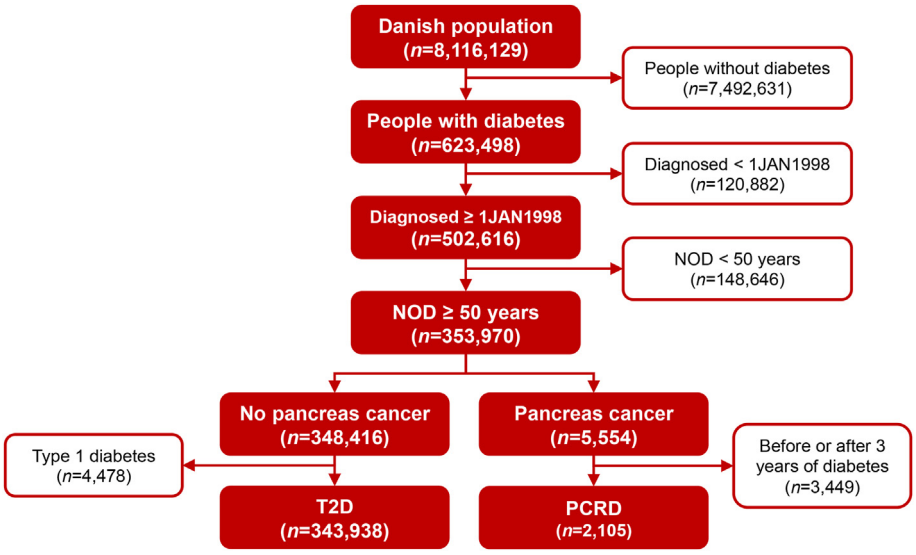

Fig. 1. Overview of people included in this study. From a total of 8,116,129 million Danish citizens, 343,938 people with T2D and 2105 people with PCRD were identified.

Table 1
Baseline characteristics of people with PCRD and T2D.

	PCRD	T2D	P-value
N	2105	343,938	
Age at diagnosis, median (IQR)	70.9 (64.1–77.3)	66.0 (58.6–74.2)	<0.0001
Age groups, n (%)			
50–59 years	266 (12.6)	101,509 (29.5)	<0.0001
60–69 years	719 (34.2)	114,914 (33.4)	
70–79 years	765 (36.3)	84,698 (24.6)	
>80 years	355 (16.9)	42,817 (12.4)	
Sex, n (%)			
Female	994 (47.3)	191,850 (44.2)	0.0057
Male	1111(52.8)	76,242 (55.8)	
Heavy smoker, n (%)	427 (20.3)	76,242 (22.2)	<0.0001
Alcohol abuse, n (%)	60 (2.9)	10,698 (3.1)	<0.0001
Highest completed education, n (%)			
≤ High-school graduate	1620 (77.0)	266,786 (77.6)	0.7295
> High-school graduate	330 (15.7)	53,187 (15.5)	
Unknown	155 (7.4)	23,965 (7.0)	
Income, n (%)			
Low	677 (32.2)	101,325 (29.5)	0.0006
Normal	1165 (55.3)	192,310 (55.9)	
High	263 (12.5)	49,091 (14.3)	
Unknown	<5	1212 (0.4)	
Comorbidities			
Obesity, n (%)	51 (2.4)	13.753 (4.0)	<0.0001
Polycystic ovarian syndrome, n (%)	0 (0)	25 (0)	–
Chronic kidney disease, n (%)	16 (0.8)	3613 (1.1)	<0.0001
Charlson Comorbidity Index, mean (SD)	1.3 (0.8)	1.4 (0.9)	0.0002
Charlson category, n (%)			
1	1657 (78.7)	262,708 (76.4)	0.0007
2	274 (13.0)	43,870 (12.8)	
>2	174 (8.3)	37,360 (10.9)	
Concomitant medications			
Antidepressants, n (%)	340 (16.2)	63,976 (18.6)	<0.0001
Opioids, n (%)	635 (30.2)	95,102 (27.7)	<0.0001
Anxiolytics, n (%)	296 (14.1)	49,690 (14.4)	<0.0001
Antihypertensives, n (%)	1407 (66.8)	247,274 (71.9)	<0.0001
Antithrombotics, n (%)	848 (40.3)	132,814 (38.6)	<0.0001
Statins, n (%)	790 (37.5)	144,609 (42.0)	<0.0001

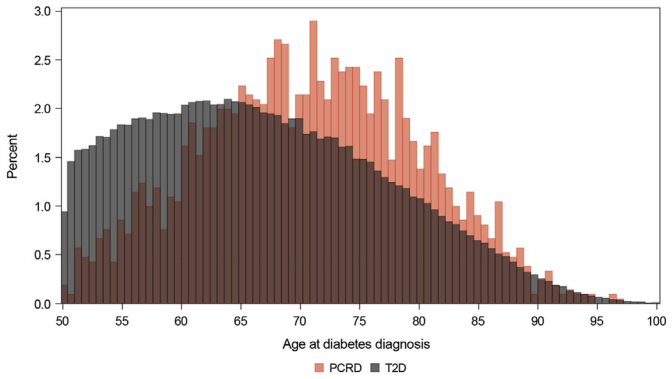

Fig. 2. Distribution of age at diabetes diagnosis among people with PCRD and T2D.

after NOD diagnosis. In people with PCRD, the plasma level of HbA1c before NOD diagnosis was characterised by a stable period in the normal glycaemic range followed by a steep incline starting approximately one year before diabetes diagnosis. In contrast, HbA1c levels gradually increased in people with T2D. Correspondingly, significant differences in median HbA1c levels between PCRD and T2D were detected up to three years before NOD diagnosis. Similarly, distinct patterns were observed for triglycerides before NOD diagnosis, with gradually declining triglyceride levels in people with PCRD and stable triglyceride levels in people with T2D. Differences in cholestatic and inflammatory markers did not differ between PCRD and T2D before NOD diagnosis. Still, they showed different trajectories after NOD onset, with increasing levels in people with PCRD and stable (normal) levels in people with T2D.

4. Discussion

In a population-based nationwide setting, the 3-year cumulative incidence of pancreatic cancer was 0.6% in people aged 50 or older with newly diagnosed diabetes. Patients with diabetes related to pancreatic cancer were generally older compared to people with T2D. In contrast, people with T2D were characterized by an increased prevalence of comorbidities and more prescriptions of medications used to treat cardiovascular diseases. Distinct changes in routine biochemical parameters were observed between diabetes subgroups. These findings attest to previous observations and expand these to a nationwide population-based setting. The distinct differences in routine biochemical parameters may help to differentiate people with cancer-related diabetes from the much more prevalent T2D.

4.1. Incidence of PDAC among people with NOD

The 3-year cumulative incidence of PDAC among people with NOD observed in our study (0.6%) differs moderately from previous observations. Hence, in the studies from Olmsted County, the cumulative 3-year incidence was 0.85% and 1.0% in two separate cohorts. Importantly, these studies were based on glycaemic-defined criteria for NOD as opposed to the epidemiological approach in our study. It is conceivable that studies based on glycaemic-defined

Table 2
Multivariable analysis of demographic and clinical characteristics and the odds of having PCRD (vs. T2D).

	Odds ratio (95% CI)	P-value
Age group		
50–59 years	1 (reference)	
60–69 years	2.62 (2.27–3.02)	<0.0001
70–79 years	4.11 (3.55–4.76)	<0.0001
>80 years	4.14 (3.46–4.95)	<0.0001
Female sex	1.12 (1.02–1.23)	0.0141
Heavy smoker	0.93 (0.83–1.04)	0.1918
Alcohol abuse	1.21 (0.93–1.57)	0.1597
Highest completed education		
≤ High-school graduate	1 (reference)	
> High-school graduate	1.08 (0.96–1.23)	0.2046
Unknown	0.81 (0.67–0.97)	0.0209
Income		
Low	1 (reference)	
Normal	1.18 (1.06–1.31)	0.0026
High	1.08 (0.92–1.27)	0.3467
Unknown	–	
Comorbidities		
Obesity	0.74 (0.56–0.98)	0.0328
Chronic kidney disease	0.89 (0.54–1.48)	0.6493
Charlson category		
1	1 (reference)	
2	0.91 (0.80–1.04)	0.1762
>2	0.64 (0.54–0.75)	<0.0001
Concomitant medications		
Antidepressants	0.86 (0.76–0.97)	0.0157
Opioids	1.21 (1.09–1.33)	0.0002
Anxiolytics	0.98 (0.88–1.12)	0.7710
Antihypertensives	0.65 (0.59–0.72)	<0.0001
Antithrombotics	1.06 (0.96–1.17)	0.2815
Statins	0.83 (0.75–0.91)	0.0001

criteria identify a larger subset of patients that may still need to reach clinical attention. On the other hand, the studies based on glycaemic defined threshold may be prone to selection bias and not be fully representative of the general population. As such, the NOD criteria devised in our study may better reflect real-world clinical practice. Indeed, by using a combination of diagnostic codes and prescriptions of glucose-lowering therapies to identify people with NOD, we could identify NOD cases from both primary care and hospital-based settings and thus estimate a cumulative incidence estimate representative of the general population. To further support this notion, two studies based on insurance databases from the United States solely based on diagnosis codes (without including information on glucose-lowering medications) reported cumulative 3-year incidence estimates well below those observed in our study (0.3%) [6,7].

4.2. Demographic and clinical characteristics of PCRD vs. T2D

In keeping with past observations, we confirmed older age as a risk factor for pancreatic cancer [1]. Likewise, we demonstrated that PCRD was more prevalent in women when using T2D as a comparator group. This finding reflects the male predominance among people with T2D [19]. The finding that people with T2D had a higher burden of comorbidities and more prescriptions of antihypertensives and statins are in keeping with the high frequency of cardiovascular comorbidities associated with the metabolic syndrome even before the diagnostic criteria for diabetes are met [20]. Finally, the observation that people with PCRD redeemed more prescriptions for opioids may be explained by the upper abdominal pain commonly associated with pancreatic cancer [21].

Table 3
Laboratory results at baseline for people with PCRD and T2D.

	PCRD	T2D	*p* value
N	2105	343,938	
Metabolism			
HbA1c, n (%)	716 (34.0)	121,350 (35.3)	
HbA1c (mmol/mol), median (IQR)	57 (50–77)	52 (48–63)	<0.0001
Total Cholesterol, n (%)	615 (29.9)	111,701 (32.5)	
Total Cholesterol (mmol/L), median (IQR)	4.5 (3.8–5.4)	4.8 (4.1–5.7)	<0.0001
HDL, n (%)	607 (28.8)	110,388 (32.1)	
HDL (mmol/L), median (IQR)	1.2 (1.0–1.5)	1.2 (1.0–1.4)	<0.0001
LDL, n (%)	478 (22.7)	81,550 (23.7)	
LDL (mmol/L), median (IQR)	2.3 (1.8–3.1)	2.6 (2.0–3.4)	<0.0001
Triglyceride, n (%)	448 (21.3)	85,635 (24.9)	
Triglyceride (mmol/L), median (IQR)	1.6 (1.2–2.4)	2.0 (1.4–2.9)	<0.0001
Liver test			
Bilirubin, n (%)	489 (23.2)	68,141 (19.8)	
Bilirubin (μmol/L), median (IQR)	9.6 (7.0–15.0)	8.0 (6.0–12.0)	<0.0001
Alkaline Phosphatase, n (%)	517 (24.6)	77,619 (22.6)	
Alkaline Phosphatase (U/L), median (IQR)	94 (73–136)	82 (67–102)	<0.0001
GGT, n (%)	301 (14.3)	40,654 (11.8)	
GGT (U/L), median (IQR)	57 (31–209)	49 (30–91)	<0.0001
INR, n (%)	310 (14.7)	42,116 (12.2)	
INR (INR unit), median (IQR)	1.0 (1.0–1.2)	1.0 (1.0–1.2)	0.9552
Nutritional status			
Haemoglobin, n (%)	623 (29.6)	107,565 (31.3)	
Haemoglobin (mmol/L), median (IQR)	8.6 (8.0–9.2)	8.9 (8.2–9.5)	<0.0001
Albumin, n (%)	509 (24.2)	76,768 (22.3)	
Albumin (g/L), median (IQR)	38 (34–42)	39 (35–42)	0.0060
Inflammation			
CRP, n (%)	508 (24.1)	76,794 (22.3)	
CRP (mg/L), median (IQR)	9.0 (3.8–24.0)	6.1 (3.0–15.4)	<0.0001
Leucocytes, n (%)	590 (28.0)	95,055 (27.6)	
Leucocytes (10^9/L), median (IQR)	7.9 (6.6–9.8)	7.8 (6.4–9.6)	0.1358
Platelets, n (%)	592 (28.1)	92,193 (26.8)	
Platelets (10^9/L), median (IQR)	246 (196–303)	249 (205–301)	0.2623

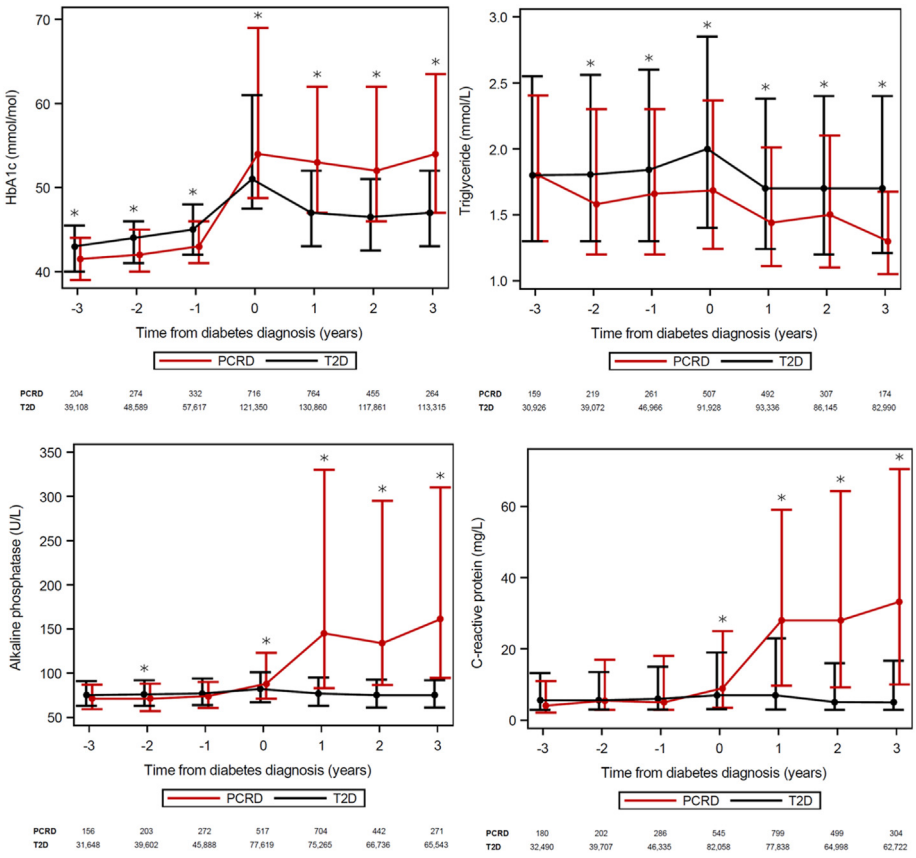

Fig. 3. Temporal changes in medians (IQR) of selected biochemical variables in people with PRCD compared to T2D. A Mann-Whitney *U* test for the difference in medians between PCRD and T2D was performed for each time point. A significant difference was marked with an asterisk if the p-value was below a Bonferroni-corrected alpha level of 0.00714.

4.3. Biochemical characteristics of PCRD vs. T2D

An important observation of our study was the distinct changes in metabolic parameters observed in people with PCRD vs. T2D before a diabetes diagnosis. These findings expand previous observations to a population-based setting and highlight that PCRD is associated with metabolic changes distinctive from T2D. Increasing blood glucose level is a well-known feature of PDAC, where the earliest changes in glycaemic signals can be observed for up to three years before diagnosis [13,17,22]. However, previous studies investigating plasma glucose and HbA1c trajectories did not include a group of people with T2D for comparison. Consequently, there are no studies to directly compare our findings with. However, our observations align with the exponentially increasing plasma glucose levels observed in pancreatic cancer patients before cancer diagnosis compared with healthy controls [17]. The mechanisms responsible for these glycaemic alterations are linked to complex mechanisms beyond tumour-induced damage of pancreatic islet cells. For example, pancreatic cancer induces insulin resistance and beta-cell dysfunction that resolve with tumour resection [3]. This implies the presence of paraneoplastic mediators from tumour cells and pancreas cancer-derived exosomes have been identified as key molecules in this context [23].

Another distinctive biochemical feature of PCRD vs. T2D was the changes in plasma triglyceride levels before the diagnosis of diabetes. Hence, in patients with PCRD, the triglyceride levels decreased gradually towards the time point for diabetes diagnosis, while they remained stable in people with T2D. This observation is in keeping with past observations and is probably related to exosome-induced browning of subcutaneous adipose tissue [3,13,17,23].

We also observed differences between PCRD and T2D in relation to cholestatic liver parameters and markers of systemic inflammation. These differences were only observed after diabetes onset. The changes in cholestatic parameters most likely reflect tumour-mediated obstruction of the biliary tract or the presence of liver metastasis [13]. The increased markers of inflammation are most likely related to the systemic inflammatory response accompanying pancreatic cancer [24].

4.4. Clinical implications

The findings from our study and previous studies suggest that NOD constitutes a target group relevant to early diagnosis of PDAC. This was recently acknowledged by the National Institutes of Health, which sponsored a large prospective cohort study planning to include 10,000 people older than 50 years with NOD to further clarify the associated risk with PDAC and to study biomarkers for early cancer detection [25]. Although these initiatives are likely to advance the understanding of PCRD and possibly identify new biomarkers to differentiate PCRD from other diabetes subtypes, the routine parameters investigated in our study may be more practical to implement in risk stratification tools targeted at the general population level. Indeed, previous studies have used changes in HbA1c and other routine biochemical parameters to differentiate between diabetes subgroups. However, the use of these models has not been widely implemented in clinical practice possible due to the need for historical data, including weight information and

biochemical parameters, assessed one year before a diabetes diagnosis. Such data are often not available in routine clinical practice. Therefore trajectory-based analysis of routine biochemical parameters, as illustrated in the present study, in combination with data engineering and artificial intelligence, may be used to develop more practical models for PCRD case finding in the future [26].

According to studies based on a systematic assessment of glycaemic parameters in PDAC, approximately 85% of patients have elevated fasting blood glucose levels, and approximately 50% have diabetes at PDAC diagnosis [27]. This highlights that glucose hemostasis disturbance is a very common observation in PDAC [3]. However, in a clinical setting, where new-onset hyperglycemia may serve as a potential indicator of PDAC, it is important to consider that the prevalence of individuals with a diagnosis of hyperglycemia or diabetes is likely to be lower. This is because hyperglycemia is often asymptomatic, particularly in its early stages. It is worth noting that the population-based number of patients with PDAC who are initially diagnosed with NOD remains unknown. Understanding the extent to which NOD serves as an initial sign of PDAC on a population-based level is an important question that requires further investigation.

4.5. Strengths and limitations

A strength of our study is the nationwide population-based design using the high-quality health registries in Denmark, including detailed information on medicine prescriptions. This allowed us to accurately identify people with NOD in a population-based setting. Also, the possibility of linking individual data to biochemical parameters on a population-based level is a unique aspect of our study.

The main limitation of this study is the risk of misclassification and lack of case verification. However, the accuracy of ICD-10 codes and the validity of the Danish health registries are generally high, with diabetes-related codes having positive predictive values above 90% [8]. Likewise, the diagnostic accuracy of PDAC diagnosis is high, with histological confirmation in more than 80% of cases [28]. Finally, in a sensitivity analysis excluding people with obesity and/or polycystic ovarian syndrome, the 3-year cumulative incidence rate of PDAC was similar to that observed in the primary analysis implicating that misclassification of diabetes was not a major issue. Another limitation is the incompleteness of biochemical parameters. Hence, the people with available biochemical parameters may be different from those without, thus introducing the possibility of selection bias. However, for the descriptive purpose of the present study, we consider this to be of little importance. Weight is an important component of most previous algorithms developed for PDAC determination in people with NOD [29,30]. Unfortunately, weight is not available in the Danish health registries which is also a limitation of our study. Finally, the Danish population is homogenous, with approximately 85% of Danish descent. Therefore, our findings must be verified in other populations with different ethnic compositions.

5. Conclusions

In a nationwide population-based setting, the 3-year cumulative incidence of PDAC is 0.6% among people 50 years or older with newly diagnosed diabetes. People with cancer-related diabetes are characterised by distinct trajectories of plasma HbA1c and triglyceride levels and distinct demographic and clinical profiles compared to people with T2D. These distinctive features, based on widely available parameters from routine clinical practice, may be used to develop risk stratification models amendable to implementation in a primary care setting.

Author contributions

M.H.J. and S.S.O researched data and wrote the manuscript. S.L.C., O.H., S.D.H. and A.M.D. contributed to the discussion and reviewed/edited the manuscript. M.H.J. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Declaration of competing interest

No potential conflicts of interest relevant to this article were reported.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pan.2023.07.001.

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