Risk of Major Adverse Cardiovascular Events, Severe Hypoglycemia, and All-Cause Mortality in Postpancreatitis Diabetes Mellitus Versus Type 2 Diabetes: A Nationwide Population-Based Cohort Study

Søren S. Olesen,[1,2] Rikke Viggers,[2,3] Asbjørn M. Drewes,[1,2,3] Peter Vestergaard,[2,3] and Morten H. Jensen[3,4]

Diabetes Care 2022;45:1326–1334 | https://doi.org/10.2337/dc21-2531

OBJECTIVE

Postpancreatitis diabetes mellitus (PPDM) is a frequent complication of pancreatitis and associates with poor glycemic control. We investigated the risk of adverse diabetes-related outcomes in PPDM compared with type 2 diabetes.

RESEARCH DESIGN AND METHODS

In this Danish population-based cohort study, we included adults (>18 years) with incident PPDM or type 2 diabetes between 1998 and 2018 through national health registries. PPDM was further divided into acute (PPDM-A) and chronic (PPDM-C) subtypes. We ascertained risk of major adverse cardiovascular events (MACE), severe hypoglycemia, and all-cause mortality as well as incidence rates of severe hypoglycemia. We compared risk and incidence rates across diabetes subgroups using multivariate Cox and Poisson regression analyses.

RESULTS

We identified 383,325 people with incident type 2 diabetes, 3,418 with PPDM-A, and 2,461 with PPDM-C. Compared with type 2 diabetes, PPDM-C was associated with increased risks of severe hypoglycemia (hazard ratio [HR] 5.27, 95% CI 4.62–6.00, $P < 0.001$) and all-cause mortality (HR 1.54, 95% CI 1.45–1.64, $P < 0.001$). Similar patterns were observed for people with PPDM-A. Incidence rate ratios (IRRs) for severe hypoglycemia were increased in both PPDM-C (IRR 7.38, 95% CI 6.75–8.08, $P < 0.001$) and PPDM-A (IRR 3.76, 95% CI 3.36–4.21, $P < 0.001$) compared with type 2 diabetes. Findings were consistent in an analysis restricted to people on insulin and in an analysis including pancreatitis patients without diabetes as comparator group.

CONCLUSIONS

Compared with type 2 diabetes, PPDM is associated with excess risk of adverse diabetes-related outcomes. This has important implications for management.

[1]Centre for Pancreatic Diseases and Mech-Sense, Department of Gastroenterology and Hepatology, Aalborg University Hospital, Aalborg, Denmark
[2]Department of Clinical Medicine, Aalborg University Hospital, Aalborg, Denmark
[3]Steno Diabetes Center North Denmark, Aalborg University Hospital, Aalborg, Denmark
[4]Department of Health Science and Technology, Aalborg University, Aalborg, Denmark

Corresponding author: Søren S. Olesen, soso@rn.dk

Received 8 December 2021 and accepted 22 February 2022

This article contains supplementary material online at https://doi.org/10.2337/figshare.19237152.

Postpancreatitis diabetes mellitus (PPDM) is a frequent complication of pancreatitis and occurs in more than half of patients during their disease course (1,2). Owing to a globally increasing pancreatitis incidence, the prevalence of PPDM has nearly tripled in the past decade and now constitutes ~1.5% of all adult diabetes cases (3,4). After type 2 diabetes, this makes PPDM one of the most prevalent types of diabetes in adults (5–7).

The prognosis and risk of adverse diabetes-related complications have only been scarcely investigated in PPDM as affected people are usually misclassified or excluded from studies in other diabetes subtypes. Also, in the clinical setting, people with PPDM are frequently misdiagnosed and treated as having type 2 diabetes (5–7). This may be problematic, as recent data indicate that people with PPDM have worse glycemic control and increased insulin requirements compared with people with type 2 diabetes (5–7). However, it remains largely undetermined whether the brittle diabetes observed in patients with pancreatic diseases translates to adverse diabetes related outcomes (1). For example, it is largely unknown whether PPDM is associated with excess risk of major adverse cardiovascular events (MACE) as seen in people with type 2 diabetes and high glycemic variability (8). Additionally, the risk of severe hypoglycemia has only been investigated in a few studies limited by small sample sizes or weakly defined comparison groups (1). Lastly, increased all-cause mortality has been reported in people with PPDM compared with type 2 diabetes, but these findings warrant verification in independent cohorts (9).

We hypothesized that people with PPDM have an excess risk of MACE, severe hypoglycemia, and all-cause mortality compared with people with type 2. In a Danish population-based cohort of people with incident PPDM and type 2 diabetes, the specific aims of the study were *1*) to investigate risk of MACE, severe hypoglycemia, and all-cause mortality in PPDM compared with type 2 diabetes, and *2*) to investigate incidence rates of severe hypoglycemia in PPDM compared with type 2 diabetes.

RESEARCH DESIGN AND METHODS

Study Design and Data Sources

We conducted a nationwide historical cohort study including all adults (>18 years) with incident diabetes diagnosed from 1 January 2000 to 31 December 2018 in Denmark. Data were extracted via the ICD-10 system and the Anatomical Therapeutic Chemical (ATC) classification system from the Danish National Patient Registry, the Central Person Registry, the Register of Causes of Death, the Population Education Register, the Income Statistics Register, and the National Pharmacological Database. Validity of the registries is generally high, with positive predictive values of >90% on average for diabetes-related disease codes and 93% for acute and 80% for chronic pancreatitis (10,11). As this was an observational study based on national health registries, an ethics committee approval was not required according to Danish legislation.

Study Cohort

The study cohort comprised all adults with diabetes diagnosed during the study period. Eligible people were categorized into three mutually exclusive diabetes subgroups (see below): type 2 diabetes, PPDM associated with acute pancreatitis (PPDM-A), and PPDM associated with chronic pancreatitis (PPDM-C). We excluded *1*) people with missing data on sex or birth date, *2*) people with type 1 diabetes, and *3*) people with a diagnosis of pancreatic cancer between 1 January 1996 and the end of follow-up.

Definition of Diabetes Subgroups

Definition of diabetes subtypes followed previous published algorithms (6,12–14). The diabetes diagnosis date (index date) was defined as the first prescription of glucose-lowering drugs used in diabetes (ATC: A10) or the first registered ICD-10 code related to diabetes (E10.x, E11.x, E12.x, E13.x, E14.x, G63.2, H28.0, H36.0, M14.2, O24, and R73). Type 1 diabetes was defined by at least one type 1 diabetes code (E10.x) and at least one prescription of insulin (A10A) and no prescription of noninsulin glucose-lowering medication (A10B); otherwise, case patients were defined as having type 2 diabetes. People with type 1 or type 2 diabetes were redefined as PPDM if they had a diagnosis of pancreatitis in the preceding 4 years to 3 months before the diabetes diagnosis, which complies with previous published criteria (3,15,16). They were further classified as PPDM-A (ICD-10: K85.x) or PPDM-C (ICD-10: K86.0 and K86.1). People with both an acute and a chronic pancreatitis diagnosis were classified as PPDM-C.

Outcomes and Follow-up

The outcomes of this study were MACE, severe hypoglycemia, and all-cause mortality. MACE is a composite outcome consisting of nonfatal acute myocardial infarctions (ICD-10: I21), nonfatal ischemic strokes (ICD-10: I51), and cardiovascular deaths (ICD-10: I00–99). The latter was based on data from the Danish Register of Causes of Death. Severe hypoglycemia was defined as a hypoglycemic episode leading to hospitalization (ICD-10: E159–162). All-cause mortality was based on information from the Danish Register of Causes of Death. To investigate the risk of the specified outcomes, we followed people from their respective index dates (date of diabetes diagnosis) to date of emigration, date of outcome, or end of follow-up (31 December 2018), whichever came first. People who died during follow-up were censored at the date of death for analysis of severe hypoglycemia. For the analysis of MACE, people who died during follow-up were censored at the date of death, unless they died of a cardiovascular event (ICD-10: I00–99).

Covariates

Information on baseline characteristics were retrieved from 1 January 1996 to the diabetes diagnosis date from ICD-10 and ATC codes. Age was calculated from date of birth to date of diabetes diagnosis. Socioeconomic factors of education and income were defined as highest completed education stratified in a high school graduate (or less) or above high school graduate and yearly gross income per person stratified in low (200,000 Danish kroner [DKK] or 30,000 U.S. dollars [USD]), normal (200,000–500,000 DKK or 30,000–75,000 USD), or high (500,000 DKK or 75,000 USD).

Alcohol abuse was defined by any of the following ICD-10 codes (T51.x, G312.x, G621, I426, K292, K70.x, K852, K860, or F10.x) and/or ATC codes (N07BB01, N07BB02, N07BB03 or N07BB05). Additional baseline characteristics included heavy smoking, obesity, cholelithiasis, history of nonfatal MACE, history of severe

Table 1—Baseline characteristics and clinical outcomes of the diabetes subgroups

	Type 2 diabetes	PPDM-A	PPDM-C
Individuals, *n*	383,325	3,418	2,461
Age, mean (SD) years	59 (17)	60 (15)	57 (12)
Age category (years), *n* (%)			
18–29	26,544 (6.9)	85 (2.5)	38 (1.5)
30–39	36,468 (9.5)	269 (7.9)	147 (6.0)
40–49	45,021 (11.7)	508 (14.9)	519 (21.1)
50–59	78,874 (20.6)	784 (22.9)	765 (31.1)
60–69	93,860 (24.5)	802 (23.5)	595 (24.2)
70–79	67,562 (17.6)	621 (18.2)	294 (11.9)
≥80	34,996 (9.1)	349 (10.2)	103 (4.2)
Sex, *n* (%)			
Female	191,278 (49.9)	1,440 (42.1)	783 (31.8)
Male	192,047 (50.1)	1,978 (57.9)	1,678 (68.2)
Heavy smokers, *n* (%)	90,157 (23.5)	1,014 (29.7)	771 (31.3)
Alcohol abuse, *n* (%)	20,938 (5.5)	787 (23.0)	1,574 (64.0)
Outcomes			
MACE, *n* (%)	41,029 (10.7)	352 (10.3)	231 (9.4)
Nonfatal acute myocardial infarctions, *n* (%)	19,157 (5.0)	164 (4.8)	122 (5.0)
Nonfatal stroke, *n* (%)	3,352 (0.9)	25 (0.7)	33 (1.3)
Cardiovascular death, *n* (%)	24,267 (6.3)	198 (5.8)	109 (4.4)
Heart failure, *n* (%)	33,059 (8.6)	279 (8.2)	139 (5.6)
Unstable angina, *n* (%)	6,739 (1.8)	68 (2.0)	37 (1.5)
Severe hypoglycemia			
Number of			
Episodes, *n* (%)	9,552 (2.5)	328 (9.6)	647 (26.3)
Individuals, *n* (%)	6,721 (1.8)	170 (5.0)	280 (11.4)
Individuals with 1 episode, *n* (%)	4,992 (1.3)	98 (2.9)	147 (6.0)
Individuals with 2 episodes, *n* (%)	1,193 (0.3)	36 (1.1)	62 (2.5)
Individuals with >2 episodes, *n* (%)	536 (0.1)	36 (1.1)	71 (2.9)
Died during follow-up, *n* (%)	105,252 (27.5)	1,203 (35.2)	1,133 (46.0)
Follow-up time (person-years)	2,640,815	18,807	13,103
Socioeconomic factors			
Highest completed education, *n* (%)			
<High-school graduate	191,682 (50.0)	1,744 (51.0)	1,261 (51.2)
>High-school graduate	187,236 (48.8)	1,644 (48.1)	1,174 (47.7)
Unknown	4,407 (1.1)	30 (0.9)	26 (1.1)
Income, *n* (%)			
Low	213,919 (55.8)	2,013 (58.9)	1,597 (64.9)
Normal	117,693 (30.7)	1,018 (29.8)	633 (25.7)
High	48,025 (12.5)	383 (11.2)	231 (9.4)
Unknown	3,688 (1.0)	<5	<5
Concomitant illnesses			
Obesity, *n* (%)	80,329 (21.0)	800 (23.4)	267 (10.8)
Cholelithiasis, *n* (%)	16,792 (4.4)	1,543 (45.1)	435 (17.7)
History of nonfatal MACE, *n* (%)	21,038 (5.5)	233 (6.8)	148 (6.0)
Chronic kidney disease, *n* (%)	3,900 (1.0)	103 (3.0)	61 (2.5)
Charlson Comorbidity Index, mean (SD)	1.7 (1.3)	2.1 (1.7)	2.3 (1.8)
Charlson category, *n* (%)			
1–2	263,789 (68.8)	1,797 (52.6)	1,108 (45.0)
>2	119,536 (31.2)	1,621 (47.4)	1,353 (55.0)
Concomitant medication			
Enzyme treatment, *n* (%)	549 (0.1)	78 (2.3)	853 (34.7)
Antidepressants, *n* (%)	28,290 (7.4)	375 (11.0)	454 (18.4)
Opioids, *n* (%)	160,491 (41.9)	2,333 (68.3)	2,077 (84.4)
Anxiolytics, *n* (%)	98,655 (25.7)	1,351 (39.5)	1,375 (55.9)
Antihypertensives, *n* (%)	234,221 (61.1)	2,303 (67.4)	1,480 (60.1)
Antithrombotics, *n* (%)	121,605 (31.7)	1,309 (38.3)	829 (33.7)
Statins, *n* (%)	116,485 (30.4)	1,115 (32.6)	611 (24.8)

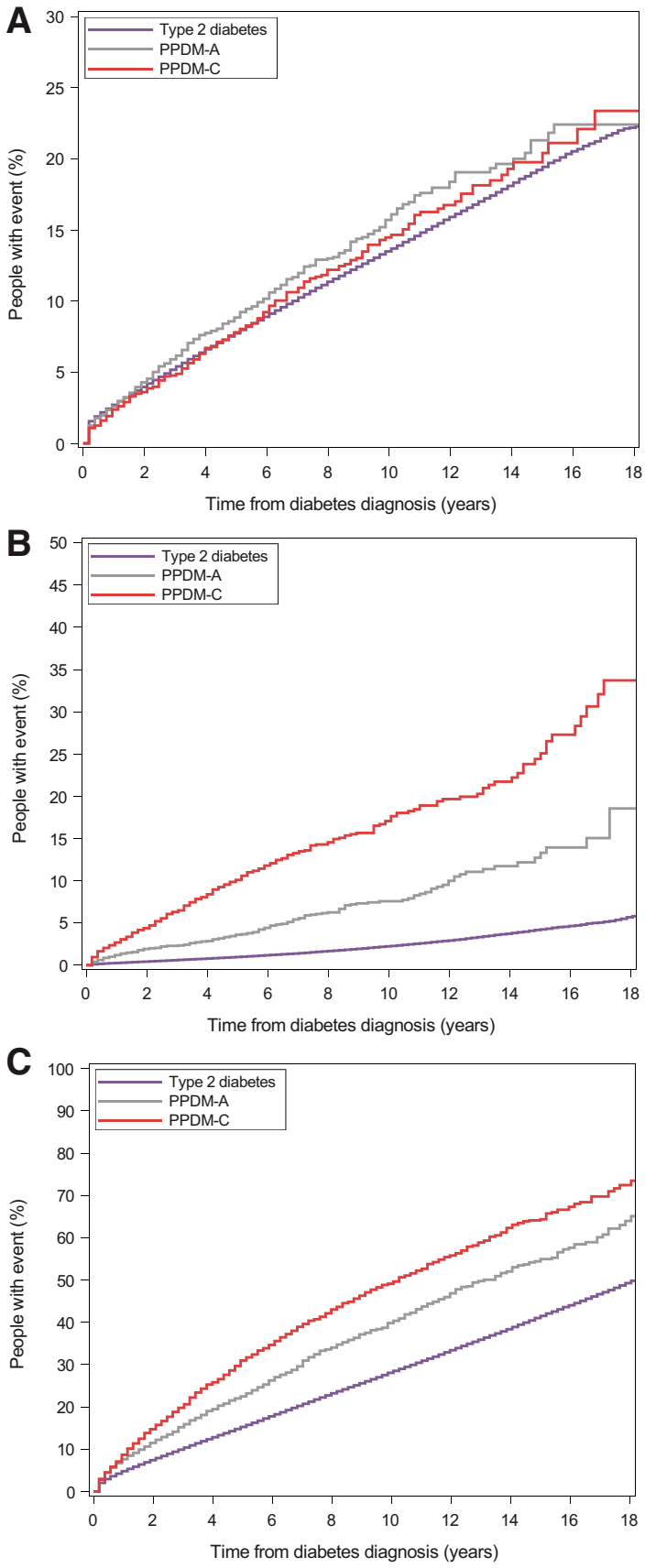

Figure 1—Time to event after diabetes for people with type 2 diabetes, PPDM-A, or PPDM-C. *A*: Time to major adverse cardiovascular event. *B*: Time to severe hypoglycemia. *C*: Time to all-cause mortality.

hypoglycemia, chronic kidney disease, enzyme treatment, antidepressants, opioids, anxiolytics, antihypertensive agents, antithrombotic agents, and statins. They were based on ICD-10 codes, ATC codes, or a combination (Supplementary Table 1) and coded as dichotomous variables. Finally, the Charlson Comorbidity Index was calculated based on ICD-10 codes (Supplementary Table 2) (17).

Statistical Analysis

Descriptive statistics are presented as means with SDs or counts and percentages of people. Crude time to each outcome for type 2 diabetes, PPDM-A, and PPDM-C, are illustrated with Kaplan-Meier curves. Adjusted effect of PPDM-A and PPDM-C versus type 2 diabetes on the outcomes were estimated with Cox proportional hazards models, and the estimates are presented in a forest plot as hazard rate ratios (HRs) with 95% CIs. Adjusted incidence rate ratios (IRRs) of PPDM-A and PPDM-C versus type 2 diabetes were estimated from Poisson regression models with $\log_e$ of person-years of exposure as offset and are presented in a forest plot as IRRs with 95% CIs. The Cox model of MACE was adjusted for age, sex, education, income, Charlson Comorbidity Index, history of nonfatal MACE, chronic kidney disease, antihypertensive agents, antithrombotic agents, statins, alcohol abuse, and heavy smoking. The Cox and Poisson models of severe hypoglycemia were adjusted for age, sex, education, income, history of nonfatal MACE, chronic kidney disease, alcohol abuse, and heavy smoking. The Cox model of all-cause mortality was adjusted for age, sex, education, income, Charlson Comorbidity Index, alcohol abuse, heavy smoking, history of nonfatal MACE, chronic kidney disease, antidepressants, opioids, anxiolytics, antihypertensive agents, anti-thrombotic agents, and statins (12). All analyses were conducted in SAS 9.4 (SAS Institute, Cary, NC) and Stata 16.1 (StataCorp, College Station, TX) software.

We performed two sensitivity analyses using similar statistical approaches as outlined above for the primary analysis. In the first sensitivity analysis, we restricted the study cohort to all adults diagnosed with diabetes in the study period receiving one or more prescriptions of insulin

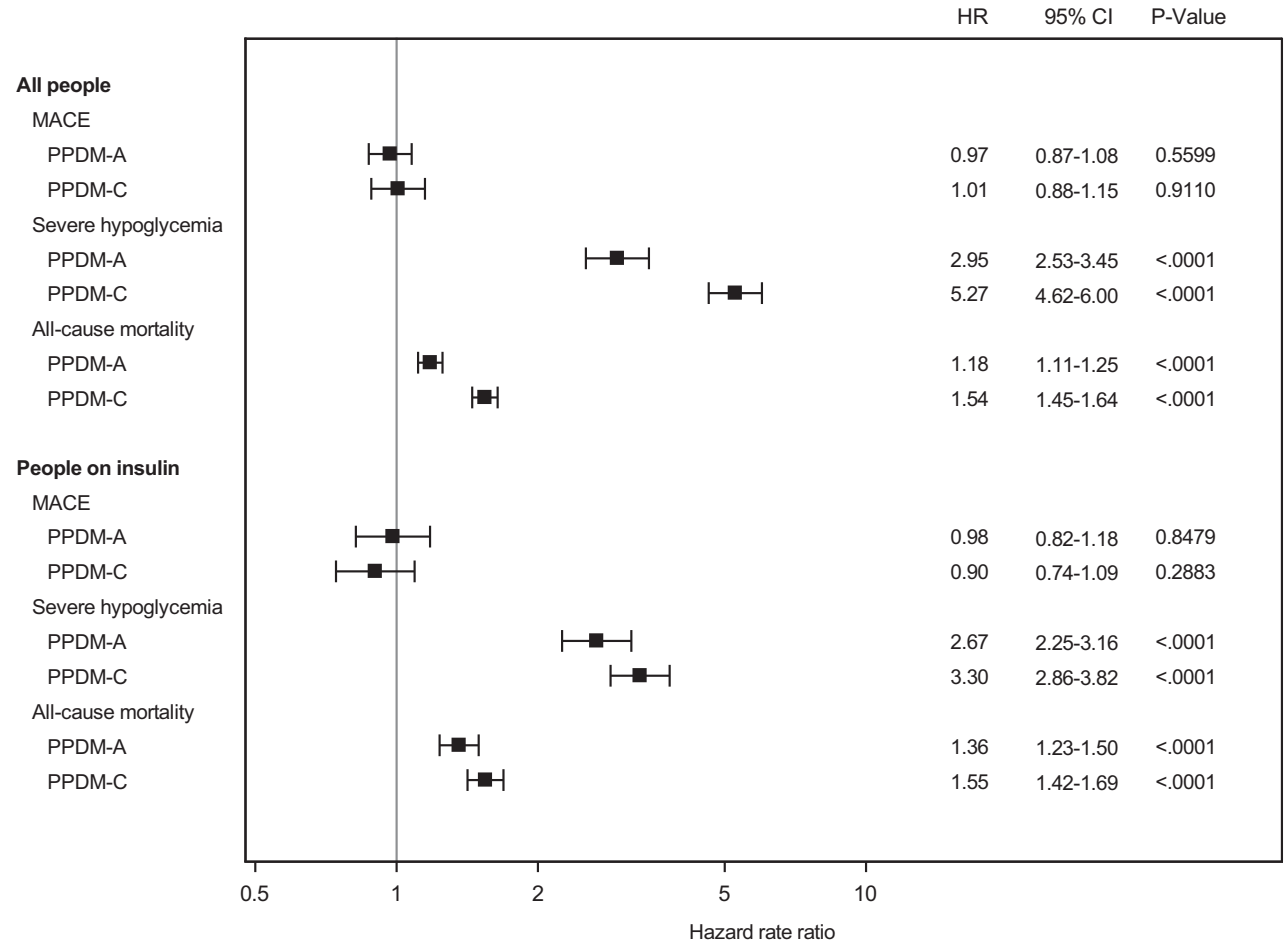

Figure 2—Forest plot showing adjusted HRs for MACE, severe hypoglycemia, and all-cause mortality in individuals with PPDM-A and PPDM-C compared with type 2 diabetes (reference group). Estimates are retrieved from Cox proportional hazards models and presented with 95% CIs and corresponding *P* values. The estimates are shown on a logarithmic scale ($\log_{10}$).

(ATC: A10A.x) during the study period ("People on insulin"). In the second sensitivity analysis, we performed a matched cohort study including comparator groups of patients with acute and chronic pancreatitis without diabetes at inclusion and who remained free of diabetes during follow-up. Acute and chronic pancreatitis patients without diabetes were matched 1:1 on year of birth and sex with PPDM-A and PPDM-C case patients, respectively. The number of PPDM case patients in this analysis was slightly lower than in the primary analysis as not all case patients could be matched with a pancreatitis patient without diabetes. This was due to a relatively low number of pancreatitis patients without diabetes during follow-up, reflecting the high incidence of diabetes in pancreatitis patients (3,18). The follow-up time for acute and chronic pancreatitis patients without diabetes started 3 months after the pancreatitis diagnosis to compensate for immortal time in the PPDM subgroups introduced by the definition of PPDM (2).

Data and Resource Availability

Data are available through Statistics Denmark (https://www.dst.dk, project identifier 703382) to authorized Danish research organizations upon request. Access for international researchers can only be gained if they are affiliated to a Danish research organization.

RESULTS

We identified 658,615 people with a diagnosis of diabetes during the study period (2000–2018). After exclusion of *1*) 246,762 individuals with prevalent diabetes, *2*) 5,490 diagnosed with pancreatic cancer during follow-up, *3*) 7,907 people <18 years of age at diabetes diagnosis, and *4*) 9,252 people classified as type 1 diabetes, the final study cohort comprised 389,204 adults with incident diabetes (Supplementary Fig. 1). Among included people, 383,325 were classified as type 2 diabetes, 3,418 as PPDM-A, and 2,461 as PPDM-C. Baseline characteristics and outcomes of the three diabetes subgroups are reported in Table 1. People with PPDM and type 2 diabetes showed similar age distributions, while a male predominance was observed in the PPDM subgroups.

Risk of MACE, Severe Hypoglycemia, and All-Cause Mortality

Kaplan-Meier curves of time to MACE, severe hypoglycemia, and all-cause mortality for the three diabetes subgroups are illustrated in Fig. 1. Compared with people with type 2 diabetes, there was an earlier and increased risk of severe hypoglycemia and death in people with PPDM-A and PPDM-C, with the most

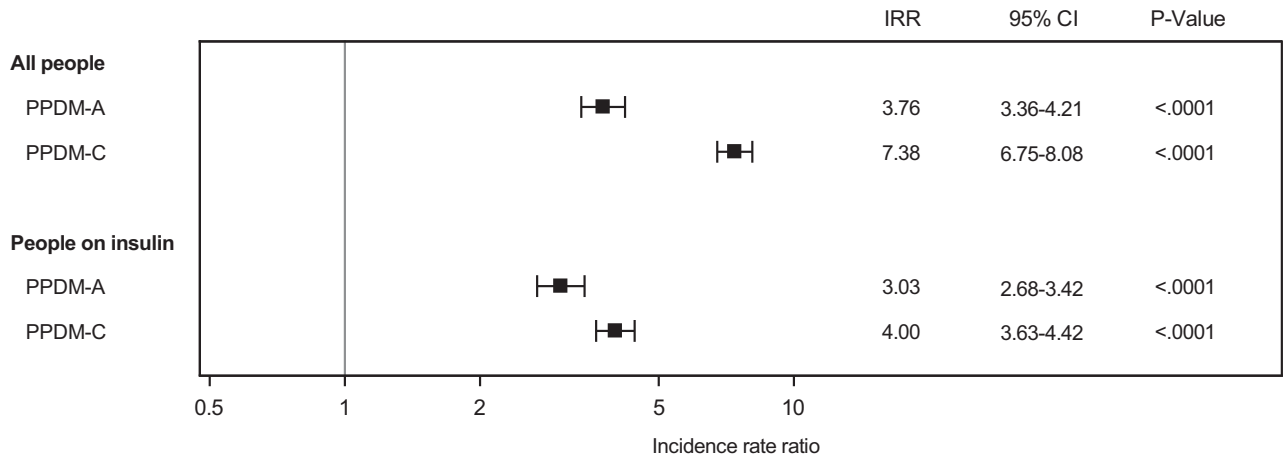

Figure 3—Forest plot showing adjusted IRRs of severe hypoglycemia for individuals with PPDM-A and PPDM-C compared with type 2 diabetes (reference group). Estimates are retrieved from Poisson regression models and reported with 95% CIs and corresponding *P* values. The estimates are shown on a logarithmic scale (log_{10}).

pronounced effects observed for the PPDM-C subgroup.

Adjusted HRs of MACE, severe hypoglycemia, and all-cause mortality in people with PPDM-A and PPDM-C compared with type 2 diabetes are illustrated in Fig. 2. Compared with type 2 diabetes, PPDM-A was associated with an increased risk of severe hypoglycemia (HR 2.95, 95% CI 2.53–3.45, $P < 0.001$) and an increased risk of all-cause mortality (HR 1.18, 95% CI 1.11–1.25, $P < 0.001$). Likewise, PPDM-C was associated with excess risk of severe hypoglycemia (HR 5.27, 95% CI 4.62–6.00, $P < 0.001$) and all-cause mortality (HR 1.54, 95% CI 1.45–1.64, $P < 0.001$). No difference in risk of MACE was observed for the PPDM-A or PPDM-C subgroups compared with type 2 diabetes (Fig. 2).

Alcohol abuse was identified as an independent risk factor for MACE (HR 1.29, 95% CI 1.24–1.35, $P < 0.001$), severe hypoglycemia (HR 2.42, 95% CI 2.23–2.61, $P < 0.001$), and all-cause mortality (HR 2.05, 95% CI 2.00–2.10, $P < 0.001$).

Incidence of Severe Hypoglycemia

Among people with PPDM-A, the mean incidence rate of severe hypoglycemia was 17.4 (95% CI 15.6–19.4) per 1,000 person-years compared with 3.6 (95% CI 3.5–3.7) per 1,000 person-years for type 2 diabetes (IRR 4.63, 95% CI 4.13–5.17, $P < 0.001$). For people with PPDM-C, the mean incidence rate of severe hypoglycemia was 49.4 (95% CI 45.7–53.2) per 1,000 person-years. This corresponds to an IRR of 13.10 (95% CI 12.08–14.19, $P < 0.001$) compared with type 2 diabetes.

Adjusted IRRs of severe hypoglycemia for people with PPDM-A and PPDM-C compared with type 2 diabetes are illustrated in Fig. 3. PPDM-A was associated with a 3.8-fold increased incidence rate of severe hypoglycemia and PPDM-C with a 7.4-fold increased incidence rate compared with type 2 diabetes.

Sensitivity Analyses

To test the influence of insulin treatment on our findings we conducted a sensitivity analysis restricted to people on insulin treatment (n = 70,577). Baseline characteristics are reported in Supplementary Table 3. As seen for the primary analysis, people with PPDM-A and PPDM-C on insulin therapy had increased risk of severe hypoglycemia and all-cause mortality compared with people with insulin-treated type 2 diabetes (Fig. 2). Although effect sizes were attenuated, the risk of severe hypoglycemia remained high, in particular for people with PPDM-C (HR 3.30, 95% CI 2.86–3.82, $P < 0.001$). In keeping with this, IRRs for severe hypoglycemia were increased in people with insulin-treated PPDM-A and PPDM-C compared with people with insulin-treated type 2 diabetes (Fig. 3).

To test whether PPDM was associated with excess risk of MACE and all-cause mortality beyond that mediated by acute and chronic pancreatitis per se, we conducted a matched cohort study. We matched PPDM-A and PPDM-C patients with acute and chronic pancreatitis patients without diabetes. Baseline characteristics are reported in Supplementary Table 4. The presence of PPDM was associated with an excess risk of MACE in both acute pancreatitis patients (HR 1.33, 95% CI 1.11–1.59, P = 0.0016) and chronic pancreatitis patients (HR 1.29, 95% CI 1.03–1.69, P = 0.027). Also, PPDM was associated with increased mortality in acute pancreatitis patients (HR 1.37, 95% CI 1.23–1.51, $P < 0.001$) and chronic pancreatitis patients (HR 1.14, 95% CI 1.11–1.26, P = 0.016) (Supplementary Fig. 2).

CONCLUSIONS

In a nationwide population-derived cohort, we investigated the risk of adverse diabetes-related outcomes in people with PPDM compared with people with type 2 diabetes. An increased risk of severe hypoglycemia and all-cause mortality was observed in people with PPDM related to both acute and chronic pancreatitis. In keeping with this, incidence rates of severe hypoglycemia were markedly elevated in PPDM compared with type 2 diabetes. Our findings were consistent in a sensitivity analysis restricted to people on insulin therapy and in a matched cohort study including acute and chronic pancreatitis patients without diabetes as comparator groups. Collectively, these observations emphasize the poorer prognosis associated with PPDM and underline the urgent need for improved and evidence-based management strategies.

MACE and PPDM

We did not observe differences in the risk of MACE between PPDM subgroups and people with type 2 diabetes. In keeping with this, distributions of single cardiovascular outcomes, including heart failure, unstable angina pectoris, and cardiovascular death, were proportionate between subgroups. These findings indicate that the cardiovascular risk in people with PPDM is comparable to that observed for type 2 diabetes. Similar observations were reported from another recent population-based study of cardiovascular risk in people with PPDM versus type 2 diabetes (9). In the sensitivity analysis, an increased risk of MACE was observed for PPDM subgroups compared with matched pancreatitis patients without diabetes. This indicates that the presence of diabetes rather than pancreatitis per se elevates risk of MACE in people with PPDM. As such, the high prevalence of diabetes in patients with chronic pancreatitis (30–40%) may explain the 1.9-fold increased cardiovascular risk observed in this population compared with age- and sex-matched control subjects from the general population (19–21).

Severe Hypoglycemia and PPDM

Although brittle diabetes and hypoglycemia is a common clinical observation in people with PPDM, as appreciated by several reviews in the field (1,2,22–24), remarkably few studies have studied the risk of severe hypoglycemia in this context and compared it to other diabetes subtypes. A recent cohort study from Taiwan based on a National Health Insurance Research Database reported a threefold increased risk of hypoglycemia in PPDM-C compared with a group of individuals with unspecified diabetes (25). This estimate is lower than the approximate fivefold increased risk of hypoglycemia observed in the PPDM-C subgroup in our study. However, the lack of information on diabetes subtypes included in the comparison group of the Taiwan study makes a direct comparison difficult. Also, the Taiwan study was limited by a relatively small sample size (506 PPDM patients) (25).

In addition to time-to-event analysis, we also calculated the incidence rate of severe hypoglycemia to investigate the "hypoglycemic burden" for individuals with PPDM. The highest incidence rate was observed for PPDM-C (~50 per 1,000 person-years) which corresponded to an approximate sevenfold increased incidence rate compared with type 2 diabetes in the adjusted analysis. There are no studies to directly compare this estimate with. In a U.S.-based study investigating the incidence of hospital admissions for hypoglycemia among Medicare beneficiaries (>65 years) with diabetes from 1999 to 2010, the observed incidence rate was 6.1 per 1,000 person-years. This estimate corresponds roughly to the incidence rate observed among people with type 2 diabetes in our study and is also in keeping with a recent study from our group investigating time trends in hypoglycemic episodes in the Danish population (26,27). Taken together, these findings implicate that the incidence rate of severe hypoglycemia is markedly increased in people with PPDM (in particular PPDM-C) compared with other diabetes subtypes.

Several mechanisms may be implicated in the elevated risk of hypoglycemia in PPDM (1). The fibroinflammatory process underlying pancreatitis results in β-cell loss and decreased insulin secretion. However, injury to pancreatic islet cells also damages α-cells and impairs glucagon secretion, which may compromise glucose counterregulation during hypoglycemia (25). Many patients with PPDM also have pancreatic exocrine insufficiency and malassimilation of intestinal nutrients, which, together with abdominal pain and other complications related to chronic pancreatitis, may compromise nutritional intake and digestion. This leads to malnutrition and depleted glycogen stores, which again compromise gluconeogenesis during fasting and may explain the frequently observed episodes of nocturnal hypoglycemia observed in people with PPDM (28–30). Also, people with type 2 diabetes and PPDM-A are characterized by peripheral insulin resistance, while patients with PPDM-C seem to have a normal peripheral insulin sensitivity compared with type 2 diabetes (7). The higher peripheral insulin sensitivity in people with PPDM-C may contribute to the excess hypoglycemia risk observed in this subgroup. Finally, excessive alcohol consumption is a well-known risk factor for pancreatitis, and the "chaotic lifestyle" associated with alcohol abuse may also compromise compliance with insulin regimens. This elevates the risk of hypoglycemia as supported by the more than twofold increased risk of hypoglycemia observed in alcohol abusers in our study.

All-Cause Mortality and PPDM

In keeping with a recent population-based study from New Zealand, we observed an increased all-cause mortality in people with PPDM compared with type 2 diabetes (9). Specifically, we observed an 18% elevated risk of death in individuals PPDM-A and a 54% excess risk of death in PPDM-C. These numbers are higher compared with the estimates reported from the New Zealand study (15% for the total PPDM cohort). Our study was not designed to investigate death causes and, as such, we cannot clarify the reasons for the increased death rate observed in our cohort. It is possible that the Danish patients had a greater burden of comorbidity or, alternatively, were at more advanced stages of chronic pancreatitis (spectrum bias). In keeping with the study from New Zealand, we intentionally excluded individuals with pancreatic cancer to avoid misdiagnosis of pancreatic cancer-related death, and, as such, pancreatic malignancy is not likely to explain this observation (9).

Study Strengths and Limitations

A major strength of our study is the high quality and validity of the Danish National Health Registers. All registers are linkable by a unique identification number that allows for virtual complete follow-up. Such high-quality real-world registry data are particularly useful for investigations of rare outcomes with time-varying nature or long latency, such as MACE and all-cause mortality.

Our study is limited by the usual limitations of a retrospective data collection and case definitions based on Health Registries. However, the diagnostic algorithms used for diabetes case finding and classification have previously been validated and used in several previous studies where they showed high validity (3,6,7,31). Taken together with the high quality of the Danish Health Registries, we therefore consider the validity of our findings to be acceptable. However, some of the case patients classified as PPDM may have had classical type 2 diabetes due to the high prevalence of type 2 diabetes in the general population and overlapping risk factors with PPDM (20,21,32,33).

Also, we carefully designed the multivariate models for each specified outcome to account for confounding from various parameters, yet we cannot exclude that residual confounding may bias some of

the analyses, as discussed above (12). In particular, the covariates relating to smoking history and alcohol abuse may be subject to information bias as patients with a smoking history or excessive alcohol use who had not developed smoking- or alcohol-related disorders would not be correctly classified in our analysis. As such, residual confounding from unmeasured alcohol or smoking exposure may be present.

Finally, our study focused on severe hypoglycemia (defined as hypoglycemia requiring hospitalization) and the retrieved estimates should be interpreted in this context. The incidence of less severe hypoglycemic episodes will need to be studied in prospective designed studies based on patient-reported outcomes preferable in combination with continuous glucose monitoring.

Conclusion

PPDM is associated with an excess risk of severe hypoglycemia and all-cause mortality compared with type 2 diabetes. These observations emphasize the poorer prognosis associated with PPDM and underline the urgent need for improved management strategies. For example, management in a multidisciplinary setting, including expertise in treatment of diabetes and pancreatitis as well as treatment of alcohol dependency, may be useful to improve outcome. Also, use of health technologies, such as continuous glucose monitoring, may be helpful, but awaits evaluation in randomized controlled trials.

Duality of Interest. P.V. has received unrestricted grants from MSD and Servier and travel grants from Amgen, Eli Lilly, Novartis, Sanofi, and Servier. M.H.J. is a former employee at Novo Nordisk and holds shares in Novo Nordisk. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. S.S.O. and M.H.J. researched data and wrote the manuscript. R.V., A.M.D., and P.V. 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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