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# Metformin Treatment is Associated with Reduced Risk of Hypoglycaemia, Major Adverse Cardiovascular Events, and All-Cause Mortality in Patients with Post-pancreatitis Diabetes Mellitus: A Nationwide Cohort Study

*Short title*: Metformin and Post-pancreatitis Diabetes Mellitus

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## ABSTRACT

**Objective:** Post-pancreatitis diabetes mellitus (PPDM) is a frequent complication of pancreatitis and is associated with an increased risk of adverse outcomes. Metformin is recommended for the treatment of PPDM, but evidence of its risk-benefit profile is limited. In a pharmaco-epidemiologic study, we investigated the association between metformin treatment and adverse outcomes in patients with PPDM.

**Design and Methods:** In a Danish nationwide population-based cohort study, we included adults (>18 years) with incident PPDM or type 2 diabetes between 2009 and 2018. PPDM was categorised into acute and chronic subtypes (PPDM-A and PPDM-C). Associations between metformin treatment and severe hypoglycaemia, major adverse cardiovascular events (MACE), and all-cause mortality were examined across the diabetes subgroups using Cox regression analysis. Treatments with metformin, insulin, and other glucose-lowering therapies were handled as time-varying exposures.

**Results:** We included 222,337 individuals with new-onset type 2 diabetes and 3,781 with PPDM, of whom 2,305 (61%) were classified as PPDM-A and 1,476 (39%) as PPDM-C. Treatment with metformin was associated with a lower risk of severe hypoglycaemia (adjusted hazard ratio (HR) 0.41, 95% confidence interval (CI) 0.27-0.62, $P<0.0001$), MACE (HR 0.74, 95% CI 0.60-0.92, $P=0.0071$), and all-cause mortality (HR 0.56, 95% CI 0.49-0.64, $P<0.0001$) in patients with PPDM. In sensitivity analyses and among individuals with type 2 diabetes, metformin treatment exhibited comparable trends of risk reduction.

**Conclusions:** Metformin is associated with a lower risk of adverse outcomes, including all-cause mortality in patients with PPDM, supporting the use of metformin as a glucose-lowering therapy for these patients.

## SIGNIFICANCE

Post-pancreatitis diabetes mellitus (PPDM) is a frequent complication of acute and chronic pancreatitis, and this unique type of secondary diabetes is often characterised by severe metabolic derangements, hypoglycaemia, and increased mortality risk. Current clinical guidelines recommend metformin as first-line therapy for PPDM and as adjunctive therapy in patients requiring insulin. However, no clinical trial has validated the risk-benefit profile of metformin in this context. In this pharmaco-epidemiologic study, we explored the effect of metformin treatment in PPDM patients. We found a significant reduction in adverse outcomes, including all-cause mortality and hypoglycaemia, associated with metformin treatment. These findings support the recommendation of using metformin in the management of PPDM, either alone or in combination with insulin.

## INTRODUCTION

Post-pancreatitis diabetes mellitus (PPDM) is a frequent complication of acute and chronic pancreatitis. The prevalence of PPDM is increasing due to a rising pancreatitis incidence, and PPDM now accounts for approximately 1.5% of adult diabetes cases (1,2). This makes PPDM one of the most prevalent diabetes subtypes in adults after type 2 diabetes (3,4). However, it has not been widely recognised, and most patients are misclassified and treated as type 2 diabetes (3). This is problematic, as PPDM is characterised by more severe metabolic derangements, frequent hypoglycaemic episodes, and increased mortality risk compared to type 2 diabetes (4–6). Thus, it is crucial to acknowledge PPDM as a distinct diabetes subtype with special requirements for management.

Clinical guidelines recommend metformin as the preferred first-line therapy for PPDM, both as a standalone treatment and in combination with insulin (7–9). However, the risk-benefit profile of metformin or any other glucose-lowering therapy has not been assessed in clinical trials in this context, and the rationale for using metformin for PPDM is primarily based on pathophysiological reasoning and experience from type 2 diabetes (10–12). This is due to the general exclusion of individuals with pancreatic diseases from trials investigating glucose-lowering therapies. For example, landmark studies like the Diabetes Control and Complications Trial and the United Kingdom Prospective Diabetes Study (UKPDS), which established the importance of glucose control in type 1 and type 2 diabetes, respectively, did not encompass individuals with pancreatic diseases (13–15). Similarly, subsequent trials evaluating treatments based on incretin and sodium-glucose cotransporter 2 inhibitors (SGLT2 inhibitors) did not include

patients with PPDM (16,17). As a result, alternative sources of information become essential to gain insights into the risk-benefit evaluation of metformin and other glucose-lowering therapies in PPDM patients.

A recent pharmaco-epidemiologic study from New Zealand found that metformin treatment (classified as ever use vs. never use) was associated with a reduction in all-cause mortality in a population-based PPDM cohort (18). However, this study did not explore the dynamic nature of treatment with glucose-lowering medication. This is important as the prescription of glucose-lowering medication, inclusive insulin, may impact metformin treatment and *vice versa*. Therefore, it is essential to consider the time-varying nature of treatment with metformin and other glucose-lowering medications. Additionally, the New Zealand study did not investigate the effects of metformin on outcomes beyond all-cause mortality (18).

We hypothesised that treatment with metformin is associated with a decreased risk of severe hypoglycaemia, major adverse cardiovascular events (MACE), and all-cause mortality in patients with PPDM. In a Danish population-based cohort of people with incident PPDM, the aim of the study was to investigate the association between metformin treatment and the risk of severe hypoglycaemia, MACE, and all-cause mortality, respectively. A population-based cohort of individuals with type 2 diabetes was included for validation.

## MATERIALS AND METHODS

*Study design and data source*

This was a nationwide retrospective cohort study including all incident cases of adult-onset diabetes in Denmark between January 1, 2009, and December 31, 2018. In Denmark, all residents have a personal, unique, and permanent civil registration number, enabling the linkage of personal data from nationwide health registers. Information for this study was obtained through the combination of the civil registration number and eight different registers. From the Danish National Patient Registry (19), information on diabetes diagnosis, a history of acute or chronic pancreatitis, comorbidities, severe hypoglycaemia, and MACE were extracted using the International Coding of Disease version 10 (ICD-10) system. Data on age, sex, and migration were obtained from the Danish Civil Registration System (20). From the National Prescription Registry (21), information on glucose-lowering drugs and other essential medications was collected via the Anatomical Therapeutic Chemical (ATC) classification system. Survival status and cause of death were gathered from the Cause of Death Register (22) and cancer diagnoses from the National Cancer Register (23). Biochemistry was extracted from the Clinical Laboratory Information Register (24) using the international Nomenclature for Properties and Units terminology. Income status and educational level information were obtained from the Income Statistics Register and the Danish Education Register based on the Danish adaptation of the International Standard Classification of Education (25,26) (Supplementary Figure S1 and Table S1).

*Study cohort*

Individuals with diabetes were identified by the presence of a prescription for glucose-lowering drugs (ATC A10) or any ICD-10 code associated with diabetes (E10.x, E11.x, E12.x, E13.x, E14.x, G63.2, H28.0, H36.0, M14.2, O24, and R73). This approach is based on a previously published algorithm (3,5,27), identifying diabetes cases in both primary care (based on drug prescriptions) and hospital-based settings (based on ICD-10 codes and drug prescriptions). The date of diabetes onset was determined as the initial occurrence of either an ICD-10 or ATC code. Individuals were excluded if they had pre-existing diabetes, were under 18 years old at the date of their diabetes diagnosis, or if diagnosed with pancreatic cancer between January 1, 1996, and the date of diabetes onset (Supplementary Figure S1).

*Classification of diabetes subtypes*

Figure 1 illustrates the study flowchart. The cohort was initially classified into type 1 and type 2 diabetes. Type 1 diabetes was identified by an insulin prescription (ATC A10A) and a diagnosis code for type 1 diabetes (ICD10 E10.x). All others were pragmatically classified as having type 2 diabetes, including all cases with a prescription of noninsulin glucose-lowering drugs (ATC A10B). Subsequently, people with type 1 or 2 diabetes were reclassified as PPDM if they had a diagnosis of pancreatitis (acute or chronic) at least three months before the diabetes diagnosis, aligning with previously published criteria for diagnosing PPDM (18,28). PPDM cases were further classified into PPDM-A (ICD-10 K85.x) or PPDM-C (ICD-10 K86.0 or K86.1). If both acute and chronic pancreatitis diagnoses were present, individuals were classified as PPDM-C. Following the exclusion of individuals with type 1 diabetes, the final cohort comprised four

diabetes subgroups: PPDM, PPDM-A (related to acute pancreatitis), PPDM-C (related to chronic pancreatitis), and type 2 diabetes (Figure 1).

*Treatment with metformin*

The primary treatment of interest was metformin. To account for the dynamic nature of metformin treatment and to mitigate the risk of immortal-time bias, treatment with metformin was introduced as a time-varying variable in the primary analysis, allowing the classification of subjects as exposed or non-exposed to vary over time (29). Dispensing of a metformin prescription (ATC A10BA) was used as a proxy for metformin treatment. Individuals were considered exposed at the time of metformin dispensation and the following 180 days. If an additional metformin prescription was dispensed during this period, participants were then considered exposed for the subsequent 180-day period following that dispensation. Conversely, if no further prescriptions were dispensed during the period, individuals were reclassified as non-exposed until a new prescription was administered (resulting in a switch back to being considered exposed), an event occurred, or the end of follow-up (Supplementary Figure S2).

*Outcomes*

Severe hypoglycaemia, MACE, and all-cause mortality were the primary outcomes of interest. Severe hypoglycaemia was defined as an episode of hypoglycaemia leading to hospitalisation (ICD-10 E15.9-E16.2). MACE was a composite endpoint comprising nonfatal acute myocardial infarction (AMI) (ICD10 I21 and I23), nonfatal stroke (ICD-10 I61, I63, and I64), and cardiovascular death (ICD-10 I00-I99). In addition, we included nonfatal AMI, nonfatal stroke, and cardiovascular death as secondary endpoints. The

study population was followed from the date of diabetes diagnosis until the occurrence of an outcome, emigration, or the end of follow-up (December 31, 2018), whichever came first.

*Covariates*

Age and treatment with insulin, incretin-based therapy (glucagon-like peptide 1 receptor agonists and dipeptidyl peptidase IV inhibitors), and sulfonylurea were included as time-varying covariates using the method described for metformin treatment (Supplementary Figure S2). Hence, glucose-lowering treatment status (insulin, incretin-based therapy, or sulfonylurea) could change every 180 days. Likewise, age was adjusted when a subject entered a new period.

Additional covariates were included as time-fixed variables. Information was obtained from January 1, 1996, until the date of diabetes diagnosis (Supplementary Figure S1). The definition of covariates is presented in Supplementary Table S1. Comorbidities were identified from the Danish National Patient Register based on ICD-10 codes and included diagnoses of obesity, cholelithiasis, history of nonfatal MACE, and chronic kidney disease (19). The Charlson Comorbidity Index (CCI) was calculated based on ICD-10 codes from the Danish National Patient Register and the National Cancer Register (Supplementary Table S2) (30). Smoking status was determined using tobacco-related ICD-10 codes and medication dispensing for tobacco dependency or obstructive pulmonary diseases after age 40. Individuals were classified as heavy smokers to avoid underestimating smoking habits, in agreement with previous register-based studies (3). Similarly, we approximated alcohol abuse based on diagnosis or prescriptions of medicine associated with alcohol-related diseases or alcohol abuse.

From the National Prescription Registry using ATC codes, treatment with insulin, incretin-based therapy, SGLT2 inhibitors, sulfonylurea, pancreatic enzyme replacement therapy, antidepressants, anxiolytics antihypertensives, antithrombotics, statins, and opioids were identified (21). Biochemistry, including haemoglobin A1c (HbA1c), High-Density Lipoprotein (HDL), Low-Density Lipoprotein (LDL) cholesterol, and triglycerides, were collected from the Clinical Laboratory Information Register (24). These analyses were collected at baseline or within a window of up to 90 days before or seven days after the baseline. Socioeconomic factors were identified through the Danish Education Register and the Income Statistics Register (25,26). Educational level was based on the highest level of education completed, and individuals were divided into two groups: those who had completed high school or lower and those who had completed education beyond high school. Income was based on yearly gross income per individual and stratified in low (30,000 U.S. dollars [USD]), normal (30,000-75,000 USD) or high (75,000 USD).

*Statistical analysis*

Descriptive statistics are presented as counts (percentages), medians (interquartile range [IQR]), or means (standard deviation [SD]). Crude and multivariate Cox regression analyses were used to analyse the association between treatment with metformin (vs. no metformin treatment) and severe hypoglycaemia, MACE, and all-cause mortality in PPDM, PPDM-A, PPDM-C, and type 2 diabetes. From these models, hazard rate ratios (HR) with 95% confidence intervals (CI) are reported. A two-sided p-value below 0.05 indicates significance. In the multivariate analysis of severe hypoglycaemia, we adjusted for sex, age (time-varying covariate), education, income,

alcohol abuse, heavy smoking, chronic kidney disease, history of nonfatal MACE, and treatment with glucose-lowering therapies including insulin, incretin-based therapy, and sulfonylurea (time-varying covariates). The multivariate model of MACE was adjusted for sex, age (time-varying covariate), education, income, alcohol abuse, heavy smoking, CCI, chronic kidney disease, history of nonfatal MACE, antihypertensives, antithrombotics, statins, and treatment with glucose-lowering therapies including insulin, incretin-based therapy, and sulfonylurea (time-varying covariates). In the multivariate model of all-cause mortality, we adjusted for age (as a time-varying covariate), sex, income, education, alcohol abuse, heavy smoking, CCI, chronic kidney disease, history of nonfatal MACE, antidepressants, antihypertensives, antithrombotics, anxiolytics, opioids, statins, and treatment with glucose-lowering therapies including insulin, incretin-based therapy, and sulfonylurea (time-varying covariates). The selection of covariates for the three multivariate models was based on previous findings (5,27).

To gain further insights into the utilisation of glucose-lowering therapies and their association with metformin treatment, we categorised the four diabetes subgroups into metformin ever-users and metformin never-users. Subsequently, we examined the distribution of treatment with insulin, incretin-based therapy, SGLT2 inhibitors, and sulfonylurea across these subgroups. Data are presented in Supplementary Table S4-S7. This analysis was used to inform the primary analysis regarding treatment with glucose-lowering therapies in the four diabetes subgroups. As treatment with SGLT2 inhibitors was very limited in the PPDM subgroups, we did not include this in the adjustment of multivariate models in the primary analysis.

Pharmaco-epidemiologic cohort studies carry a risk of reverse causation. To address this, we conducted a sensitivity analysis limited to individuals with a follow-up of at least 180 days for all three outcomes (severe hypoglycaemia, MACE, and all-cause mortality). Crude and multivariate Cox regression analyses, like primary analyses, were conducted.

All data management and analyses were performed using SAS 9.4 (SAS Institute), Stata 17.0 (StataCorp), and Rstatistics 4.3.2 (R Development Core Team).

## RESULTS

From January 2009 to December 2018, we identified 610,839 individuals with diabetes. After excluding 375,155 with prevalent diabetes, 4,478 below 18 years of age at diagnosis, and 911 with pancreatic cancer, the cohort comprised 230,295 incident cases of adult-onset diabetes. A total of 4,177 individuals with type 1 diabetes were excluded from the final cohort as they are not generally treated with metformin. The resulting final cohort comprised 226,118 participants. Among these, 222,337 (98.3%) were classified as type 2 diabetes and 3,781 (1.7%) as PPDM. The PPDM subgroup was further divided into PPDM-A (2,305 [1.0%]) and PPDM-C (1,476 [0.7%]). A study flow chart is presented in Figure 1. Table 1 shows the baseline characteristics and outcomes of the four diabetes subgroups. People with PPDM and type 2 diabetes had similar age distributions, while a male predominance was observed in the PPDM subgroups. Patients with PPDM generally had more comorbidities and a higher prevalence of excessive alcohol consumption and heavy smoking.

*Associations between metformin treatment and all-cause mortality*

In the PPDM subgroup, 966 (25.6%) patients died during a median follow-up of 3.7 (IQR 5.0) years. Among the individuals who died, 605 (66.6%) did not receive treatment with metformin at the time of death. Table 2 and Figure 2 present the HRs for the primary outcomes. Treatment with metformin in PPDM patients was associated with a reduced risk of mortality (HR 0.53; 95% CI 0.46-0.60; *P* <0.0001), which remained statistically significant after adjusting for covariates (HR 0.56; 95% CI 0.49-0.64; *P* <0.0001). When analysing PPDM-A and PPDM-C separately, metformin treatment remained significantly associated with a lower risk of all-cause mortality in both the crude and adjusted analyses. These findings were comparable to those observed in individuals with type 2 diabetes, where treatment with metformin was associated with a significant reduction in mortality risk (adjusted HR 0.52; 95% CI 0.50-0.53; *P* <0.0001) (Table 2 and Figure 2). In the sensitivity analysis constrained to long-term follow-up (≥180 days), the lower risk of all-cause mortality associated with metformin treatment remained significant across all four subgroups in both the crude and adjusted analyses (Supplementary Table S3).

*Associations between metformin treatment and severe hypoglycaemia*

In the PPDM subgroup, 134 (3.5%) individuals with PPDM experienced an event of severe hypoglycaemia during a median follow-up of 3.5 (IQR 4.9) years. Of 279 events, 109 (39.0%) were observed in the PPDM-A subgroup and 170 (61.0%) in the PPDM-C subgroup. Of the individuals who experienced an event of severe hypoglycaemia, 104 (77.6%) did not receive treatment with metformin at the time of the event. Metformin treatment in patients with PPDM was associated with a significant reduction in the risk of severe hypoglycaemia in both crude and adjusted analyses (adjusted HR 0.41; 95%

CI 0.27-0.62; *P* <0.0001) (Table 2 and Figure 2). Reduced risk of severe hypoglycaemia in patients treated with metformin was also observed in the PPDM-A and PPDM-C subgroups. Likewise, metformin treatment was associated with a decreased risk of severe hypoglycaemia in people with type 2 diabetes, albeit to a lesser extent than in PPDM (adjusted HR 0.64; 95% CI 0.57-0.73; *P* <0.0001). In the sensitivity analysis restricted to long-term follow-up (≥180 days), the significant decrease in the risk of severe hypoglycaemia associated with metformin treatment remained significant across all four subgroups in the crude analysis. In the multivariate analysis, the association remained significant in the PPDM and type 2 diabetes subgroups (Supplementary Table S3).

*Associations between metformin treatment and MACE*

In the PPDM subgroup, 375 (9.9%) individuals experienced a MACE during a median follow-up period of 3.3 (IQR 4.8) years. Among those affected by MACE, 208 (55.5%) individuals were not treated with metformin at the time of the event. Treatment with metformin was associated with a significantly reduced risk of MACE in both crude and adjusted analyses (adjusted HR 0.74; 95% CI 0.60-0.92, *P* = 0.0071) (Table 2 and Figure 2). In the PPDM-C subgroup, treatment with metformin remained associated with reduced MACE risk (adjusted HR 0.58; 95% CI 0.40-0.84; *P* = 0.0035), but not in the PPDM-A subgroup. Further analysis of individual cardiovascular outcomes revealed that metformin treatment was associated with a lower risk of nonfatal stroke in the PPDM and PPDM-C subgroups but not a lower risk of nonfatal AMI or cardiovascular death (Table 2). In people with type 2 diabetes, treatment with metformin was also associated with a decreased risk of MACE, including a lower risk of nonfatal AMI, nonfatal stroke,

and cardiovascular death (Table 2 and Figure 2). In the sensitivity analysis constrained to long-term follow-up (≥180 days), the association between metformin use and a lower risk of MACE remained significant only in people with type 2 diabetes (Supplementary Table S3).

## DISCUSSION

In a nationwide Danish population-based cohort, we investigated the therapeutic effects of metformin in patients with PPDM and type 2 diabetes. Our findings revealed a significant reduction in the risk of all-cause mortality and severe hypoglycaemia associated with metformin treatment among individuals with PPDM and its acute and chronic subtypes (PPDM-A and PPDM-C). Additionally, we observed a lower risk of MACE in PPDM patients receiving metformin treatment, primarily driven by a reduced risk of stroke. Our study also confirmed the previously reported beneficial effects of metformin treatment in people with type 2 diabetes.

### *All-cause mortality*

In keeping with the study from New Zealand (18), we observed an association between metformin treatment and decreased risk of all-cause mortality in PPDM. Notably, our study expanded on the previous research by including a larger PPDM population and employing a more robust analysis that accounted for metformin as a time-varying treatment, thereby mitigating the impact of immortal-time bias. Additionally, we observed the beneficial effects of metformin in diabetes related to acute and chronic pancreatitis, with comparable estimates for these two PPDM subgroups. Our study also

confirmed reduced all-cause mortality risk in metformin-treated type 2 diabetes, consistent with previous research (12,31). While the underlying reasons for the reduced mortality risk remain complex and multifaceted, it is recognised that the impact of metformin extends beyond glycaemic control and the reduction of microvascular complications (12). Intriguing theories propose that metformin influences mortality reduction through mechanisms such as anti-inflammatory and anti-neoplastic pathways, among others (11,32).

*Hypoglycaemia*

This study is the first to observe a significant decrease in hypoglycaemic risk among PPDM patients treated with metformin. Our findings also indicate a decreased risk of hypoglycaemia associated with metformin treatment in individuals with type 2 diabetes, consistent with prior research (33). In patients with pancreatitis, pancreatic islet cell injury impairs the secretion of pancreatic polypeptide (34), leading to hepatic insulin resistance and increased gluconeogenesis (34,35). Consequently, blood glucose levels rise, increasing the need for glucose-lowering therapy, including insulin, which may increase the risk of hypoglycaemia. Hepatic gluconeogenesis can be inhibited by metformin, potentially reducing insulin requirements (10,36). Thus, the reduced hypoglycaemic risk attributed to metformin in PPDM is most likely a result of an insulin-sparing effect mediated by the inhibition of excessive hepatic gluconeogenesis (36). PPDM patients, particularly those with PPDM-C, have several additional risk factors that compound the risk of hypoglycaemia compared to people with type 2 diabetes (5). These include pain and exocrine pancreatic insufficiency, leading to decreased nutritional intake, malnutrition, and depleted glycogen stores. Additionally, alcohol

abuse, polypharmacy arising from multiple comorbidities, and diminished counter-regulatory glucagon response to hypoglycaemia due to inflammation-induced damage to pancreatic islets may also increase hypoglycaemic risk (4,34). This highlights the importance of multidisciplinary strategies for preventing hypoglycaemia in PPDM.

*MACE*

Findings from this study are the first to show an association between metformin treatment and cardiovascular outcomes in individuals with PPDM. We found a significantly reduced risk of MACE associated with metformin treatment in both PPDM and type 2 diabetes. Short-term glucose variability is one potential risk factor for adverse cardiovascular outcomes (37). This is particularly noteworthy for individuals with PPDM, who are often characterised by "brittle diabetes" with significant variations in blood glucose levels (4). Metformin treatment might enhance glucose stability in PPDM patients and, thus, reduce their risk of MACE, as demonstrated in our study. In the UKPDS study (31), which focused on metformin use in type 2 diabetes, researchers examined the effect of metformin on the three MACE endpoints: nonfatal AMI, nonfatal stroke, and cardiovascular-related death. They found a beneficial effect of metformin use on nonfatal AMI and cardiovascular-related death but not nonfatal stroke (31). This is comparable to the observations for people with type 2 diabetes in the present study. Intriguingly, our study observed opposite associations in the PPDM subgroup, with metformin decreasing the risk for nonfatal stroke. In contrast, no associations were observed for nonfatal AMI or cardiovascular death. The dissimilarity between type 2 diabetes and PPDM in pathophysiology, underlying mechanisms, and metabolic risk factors may account for this disparity (38,39).

*Study Strengths and Limitations*

A key strength of this study is the robustness and validity of the Danish National Health Registers (19,20). The National Prescription Registry is an added advantage, allowing a thorough exploration of metformin's impact on clinical outcomes. Danish pharmacies legally record all dispensed prescriptions, ensuring registry precision and data granularity for modelling time-varying medication exposure (21). We acknowledge the inherent limitations of retrospective data collection and the use of case definitions based on health registries, which can introduce the possibility of misclassification. To mitigate this, we used validated classifications of PPDM and type 2 diabetes. The diagnostic algorithms utilized for identifying and classifying diabetes cases have been validated in multiple studies, demonstrating high accuracy (3,5,27,38). This study population closely resembles the distribution of diabetes subtypes identified in these studies. Additionally, the Danish health registries have confirmed the accuracy of ICD-10 codes for acute and chronic pancreatitis, with a positive predictive value of 97.3% for acute pancreatitis (K85.x) and 83.1% for chronic pancreatitis (K86.0 or K86.1) (40). Another limitation of this study is the use of metformin dispensing as a proxy for metformin treatment without having detailed information on compliance or dosage. As a result, we are unable to provide any insights into the dose-related effects of metformin treatment, which would have been of considerable interest. Furthermore, the use of an observational study design, as opposed to randomised controlled trials, can introduce bias, including the issue of reverse causation (i.e., metformin being prescribed to patients with milder diabetes). Consequently, the observed lower occurrences of hypoglycaemia, MACE, and all-cause mortality may reflect the comparatively less severe nature of the disease

in these patients rather than a direct consequence of metformin. To address these concerns, we have detailed the main covariates of both metformin ever-users and never-users in Supplementary Tables S4-S7. We have made efforts to mitigate the potential differences between ever-users and never-users by adjusting for these covariates. It is crucial to note that in our analysis, we refrain from categorising participants solely as never-users or ever-users of metformin due to the time-varying nature of exposure, potentially equalising the observed differences. In addition, we have addressed the potential risk of reverse causation by conducting a sensitivity analysis specifically focused on long-term follow-up. This has yielded results that consistently support the main findings.

*Conclusion*

Metformin treatment is associated with a significantly lower risk of adverse outcomes, including all-cause mortality and hypoglycaemia in patients with PPDM. These findings support the use of metformin as a glucose-lowering therapy in these patients, either alone or in combination with insulin.


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*Conflict of Interest*

M.H.J. is an employee at Novo Nordisk and holds shares in Novo Nordisk. Co-author F.K.K. is on the editorial board of EJE. He was not involved in the review or editorial process for this paper, on which he is listed as author. No other potential conflicts of interest relevant to this article were reported.

*Data and Resource Availability*

The dataset, anonymised by Statistics Denmark (https://www.dst.dk, project identifier 708466), is available to authorised Danish research organisations upon application. Our study protocol aligns with the ethical guidelines in the 1975 Declaration of Helsinki. Importantly, epidemiological studies conducted in Denmark do not mandate ethics committee approval.

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## FIGURE LEGENDS

**Figure 1**: Flow chart of the study group classification process.
*Type 1 diabetes is not included in the final cohort as they do not generally receive metformin treatment.
*Abbreviations:* PPDM, post-pancreatitis diabetes mellitus; PPDM-APPDM related to acute pancreatitis; PPDM-C, PPDM related to chronic pancreatitis.

**Figure 2**. Forest plot showing adjusted HRs for associations between metformin prescription and all-cause mortality, severe hypoglycaemia, and MACE.
*Abbreviations:* CI, confidence interval; HR, hazard rate ratio; MACE, major adverse cardiovascular event; PPDM, post-pancreatitis diabetes mellitus; PPDM-A, PPDM related to acute pancreatitis; PPDM-C, PPDM related to chronic pancreatitis.

**Table 1.** Baseline characteristics and clinical outcomes of the diabetes subgroups.

| | PPDM | PPDM-A | PPDM-C | Type 2 diabetes |
|---|---|---|---|---|
| **Individuals, n** | 3,781 | 2,305 | 1,476 | 222,337 |
| **Age, mean (SD) years** | 60 (14) | 61 (15) | 59 (12) | 58 (17) |
| **Age category (years), n (%)** | | | | |
| 18 – 29 | 84 (2.2) | 64 (2.8) | 20 (1.4) | 17,092 (7.7) |
| 30 – 39 | 213 (5.6) | 163 (7.1) | 50 (3.4) | 21,555 (9.7) |
| 40 - 49 | 579 (15.3) | 320 (13.9) | 259 (17.6) | 26,586 (12.0) |
| 50 - 59 | 933 (24.7) | 487 (21.1) | 446 (30.2) | 44,746 (20.1) |
| 60 – 69 | 1,002 (26.5) | 580 (25.2) | 422 (28.6) | 54,804 (24.7) |
| 70 – 79 | 652 (17.2) | 445 (19.3) | 207 (14.0) | 38,921 (17.5) |
| ≥ 80 | 318 (8.4) | 246 (10.7) | 72 (4.9) | 18,633 (8.4) |
| **Female sex, n (%)** | 1,490 (39.4) | 1,015 (44.0) | 475 (32.2) | 110,940 (49.9) |
| **Heavy smokers, n (%)** | 1,639 (43.4) | 919 (39.9) | 720 (48.8) | 60,704 (27.3) |
| **Alcohol abuse, n (%)** | 1,516 (40.1) | 545 (23.6) | 971 (65.8) | 14,632 (6.6) |
| **Outcomes** | | | | |
| All-cause mortality | 966 (25.6) | 515 (22.3) | 451 (30.6) | 32,406 (14.6) |
| Severe Hypoglycaemia* | | | | |
| Total hypoglycaemic episodes, n | 279 | 109 | 170 | 1,484 |
| Persons, n (%) | 134 (3.5) | 52 (2.3) | 82 (5.6) | 1,117 (0.5) |
| Persons with 1 episode, n (%) | 75 (2.0) | 28 (1.2) | 47 (3.2) | 891 (0.4) |
| Persons with 2 episodes, n (%) | 25 (0.7) | 10 (0.4) | 15 (1.0) | 158 (0.1) |
| Persons with >2 episodes, n (%) | 34 (0.9) | 14 (0.6) | 20 (1.4) | 68 (0.0) |
| MACE | 375 (9.9) | 232 (10.1) | 143 (9.7) | 19,030 (8.6) |
| Nonfatal AMI | 109 (2.9) | 67 (2.9) | 42 (2.9) | 5,818 (2.6) |
| Nonfatal stroke | 187 (5.0) | 105 (4.6) | 82 (5.6) | 9,079 (4.1) |
| Cardiovascular death | 144 (3.8) | 100 (4.3) | 44 (3.0) | 7,877 (3.5) |
| Pancreatic cancer, n (%) | 65 (1.7) | 40 (1.7) | 25 (1.7) | 1,317 (0.6) |
| Follow-up time (person-years) | 15,306 | 9,502 | 5,804 | 1,035,564 |
| **Socioeconomic factors** | | | | |
| Highest completed education, n (%) | | | | |
| ≤ High-school graduate | 3,112 (82.3) | 1,870 (81.1) | 1,242 (84.2) | 167,094 (75.2) |
| > High-school graduate | 565 (14.9) | 365 (15.8) | 200 (13.6) | 48,688 (21.9) |
| Unknown | 104 (2.8) | 70 (3.0) | 34 (2.3) | 6,555 (3.0) |
| Income, n (%) | | | | |
| Low | 633 (16.7) | 418 (18.1) | 215 (14.6) | 43,408 (19.5) |
| Normal | 2,649 (70.1) | 1,579 (68.5) | 1,070 (72.5) | 144,174 (64.8) |
| High | 499 (13.2) | 308 (13.4) | 191 (12.9) | 33,015 (14.9) |
| Unknown | <5 | <5 | <5 | 1,740 (0.8) |
| **Concomitant illnesses** | | | | |
| Obesity, n (%) | 476 (12.6) | 372 (16.1) | 104 (7.05) | 24,734 (11.1) |

| | PPDM | PPDM-A | PPDM-C | Type 2 diabetes |
|---|---|---|---|---|
| Cholelithiasis, n (%) | 1,496 (39.6) | 1,169 (50,7) | 327 (22.2) | 13,261 (6.0) |
| History of nonfatal MACE, n (%) | 482 (12.8) | 285 (12.4) | 197 (13.4) | 23,563 (10.6) |
| Chronic kidney disease, n (%) | 121 (3.2) | 81 (3.5) | 40 (2.7) | 2,722 (1.2) |
| CCI, median (IQR) | 2 (2) | 2 (2) | 2 (2) | 1 (1) |
| Charlson category, n (%) | | | | |
| 1-2 | 2,431 (64.3) | 1,551 (67.3) | 880 (59.6) | 178,729 (80.4) |
| >2 | 1,350 (35.7) | 754 (32.7) | 596 (40.4) | 43,608 (19.6) |
| **Concomitant medications** | | | | |
| Enzyme treatment, n (%) | 605 (16.0) | 52 (2.3) | 553 (37.5) | 393 (0.2) |
| Antidepressants, n (%) | 1,869 (49.4) | 1,025 (44.5) | 844 (57.2) | 71,002 (31.9) |
| Opioids, n (%) | 2,952 (78.1) | 1,653 (71.7) | 1,299 (88.0) | 106,393 (47.9) |
| Anxiolytics, n (%) | 1,767 (43.7) | 939 (50.7) | 828 (56.1) | 60,413 (27.2) |
| Antihypertensives, n (%) | 2,630 (69.6) | 1,635 (70.9) | 995 (67.4) | 139,308 (62.7) |
| Antithrombotics, n (%) | 1,524 (40.3) | 911 (39.5) | 613 (41.5) | 73,684 (33.1) |
| Statins, n (%) | 1,380 (36.5) | 893 (38.7) | 487 (33.0) | 84,371 (38.0) |
| **Biochemistry** | | | | |
| HbA1c, mean % (mean mmol/mol) | 8.1 (65.3) | 8.0 (64.3) | 8.3 (67.0) | 7.7 (60.8) |
| HbA1c, missing values (%) | 1,783 (47.2) | 1,077 (46.7) | 706 (47.8) | 117,588 (52.9) |
| Lipids | | | | |
| Total Cholesterol mmol/L, mean (SD) | 5.8 (5.0) | 5.9 (5.2) | 5.5 (4.8) | 5.7 (4.4) |
| Total Cholesterol, missing values (%) | 2,275 (60.2) | 1,362 (59.1) | 913 (61.9) | 136,625 (61.4) |
| HDL mmol/L, mean (SD) | 1.9 (2.5) | 1.9 (2.6) | 1.9 (2.5) | 1.9 (2.5) |
| HDL, missing values (%) | 2,242 (59.3) | 1,335 (57.9) | 907 (61.4) | 133,239 (59.9) |
| LDL mmol/L, mean (SD) | 3.9 (5.0) | 4.1 (5.2) | 3.6 (4.7) | 3.9 (4.6) |
| LDL, missing values (%) | 2,408 (63.7) | 1,447 (62.8) | 961 (65.1) | 142,330 (64.0) |
| Triglyceride mmol/L, mean (SD) | 2.9 (3.5) | 2.9 (3.5) | 2.6 (3.4) | 2.6 (2.7) |
| Triglyceride, missing values (%) | 2,322 (61.4) | 1,394 (60.5) | 928 (62.9) | 139,969 (63.0) |

*Hypoglycaemia leading to hospitalisation

*Abbreviations*: AMI, acute myocardial infarction; CCI, Charlson Comorbidity Index; HbA1c, haemoglobin A1c; IQR, interquartile range; n, number of observations; MACE, major adverse cardiovascular event; PPDM, postpancreatitis diabetes mellitus; PPDM-A, PPDM related to acute pancreatitis; PPDM-C, PPDM related to chronic pancreatitis; SD, standard deviation.

**Table 2.** Association between prescription of metformin (vs no metformin) and all-cause mortality, severe hypoglycaemia, MACE, and selected cardiovascular outcomes.

| | PPDM | | PPDM-A | | PPDM-C | | Type 2 diabetes | |
|---|---|---|---|---|---|---|---|---|
| | HR (95% CI) | *P* | HR (95% CI) | *P* | HR (95% CI) | *P* | HR (95% CI) | *P* |
| **All-cause mortality** | | | | | | | | |
| Crude | 0.53 (0.46-0.60) | <0.0001 | 0.49 (0.41-0.58) | <0.0001 | 0.63 (0.52-0.76) | <0.0001 | 0.47 (0.46-0.48) | <0.0001 |
| Adjusted* | 0.56 (0.49-0.64) | <0.0001 | 0.55 (0.46-0.67) | <0.0001 | 0.60 (0.48-0.73) | <0.0001 | 0.52 (0.50-0.53) | <0.0001 |
| **Severe hypoglycaemia** | | | | | | | | |
| Crude | 0.30 (0.20-0.45) | <0.0001 | 0.32 (0.17-0.60) | 0.0003 | 0.36 (0.21-0.62) | 0.0002 | 0.56 (0.50-0.63) | <0.0001 |
| Adjusted† | 0.41 (0.27-0.62) | <0.0001 | 0.38 (0.19-0.74) | 0.0042 | 0.45 (0.26-0.79) | 0.0053 | 0.64 (0.57-0.73) | <0.0001 |
| **MACE** | | | | | | | | |
| Crude | 0.79 (0.64-0.97) | 0.0218 | 0.82 (0.64-1.07) | 0.1449 | 0.72 (0.51-1.03) | 0.0696 | 0.64 (0.63-0.66) | <0.0001 |
| Adjusted‡ | 0.74 (0.60-0.92) | 0.0071 | 0.87 (0.65-1.15) | 0.3306 | 0.58 (0.40-0.84) | 0.0035 | 0.56 (0.54-0.58) | <0.0001 |
| **Nonfatal AMI** | | | | | | | | |
| Crude | 1.06 (0.73-1.55) | 0.7474 | 1.34 (0.82-2.20) | 0.2425 | 0.74 (0.39-1.40) | 0.3539 | 0.77 (0.73-0.81) | <0.0001 |
| Adjusted‡ | 1.01 (0.68-1.52) | 0.9502 | 1.36 (0.79-2.32) | 0.2645 | 0.63 (0.31-1.25) | 0.1823 | 0.61 (0.58-0.65) | <0.0001 |
| **Nonfatal stroke** | | | | | | | | |
| Crude | 0.69 (0.51-0.92) | 0.0115 | 0.73 (0.50-1.08) | 0.1110 | 0.68 (0.42-1.08) | 0.1045 | 0.63 (0.61-0.66) | <0.0001 |
| Adjusted‡ | 0.66 (0.48- | 0.0073 | 0.84 (0.55-1.27) | 0.4037 | 0.53 (0.32-0.86) | 0.0089 | 0.54 (0.52-0.57) | <0.0001 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 0.89) | | | | | | | |
| **Cardiovascular death** | | | | | | | | |
| Crude | 0.67 (0.48-0.93) | 0.0180 | 0.55 (0.37-0.81) | 0.0030 | 0.92 (0.50-1.68) | 0.7795 | 0.49 (0.47-0.52) | <0.0001 |
| Adjusted‡ | 0.75 (0.52-1.08) | 0.1218 | 0.71 (0.45-1.11) | 0.1287 | 0.87 (0.46-1.65) | 0.6741 | 0.57 (0.54-0.60) | <0.0001 |

*Adjusted for age (as a time-varying covariate), sex, income, education, alcohol abuse, heavy smoking, CCI, chronic kidney disease, history of nonfatal MACE, antidepressants, antihypertensives, antithrombotics, anxiolytics, opioids, statins, and treatment with glucose-lowering therapies including insulin, incretin-based therapy, and sulfonylurea (time-varying covariates).

†Adjusted for sex, age (time-varying covariate), education, income, alcohol abuse, heavy smoking, chronic kidney disease, history of nonfatal MACE, and treatment with glucose-lowering therapies including insulin, incretin-based therapy, and sulfonylurea (time-varying covariates).

‡Adjusted for sex, age (time-varying covariate), education, income, alcohol abuse, heavy smoking, CCI, chronic kidney disease, history of nonfatal MACE, antihypertensives, antithrombotics, statins, and treatment with glucose-lowering therapies including insulin, incretin-based therapy, and sulfonylurea (time-varying covariates).

*Abbreviations:* AMI, acute myocardial infarction; CI, confidence interval; HR, hazard rate ratio; MACE, major adverse cardiovascular event; PPDM, post-pancreatitis diabetes mellitus; PPDM-A, PPDM related to acute pancreatitis; PPDM-C, PPDM related to chronic pancreatitis.

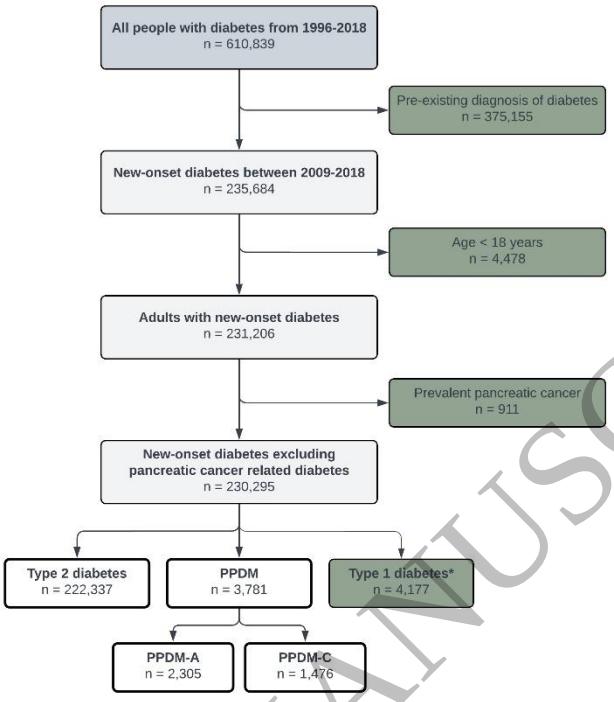


*Figure 1*
*159x130 mm (DPI)*

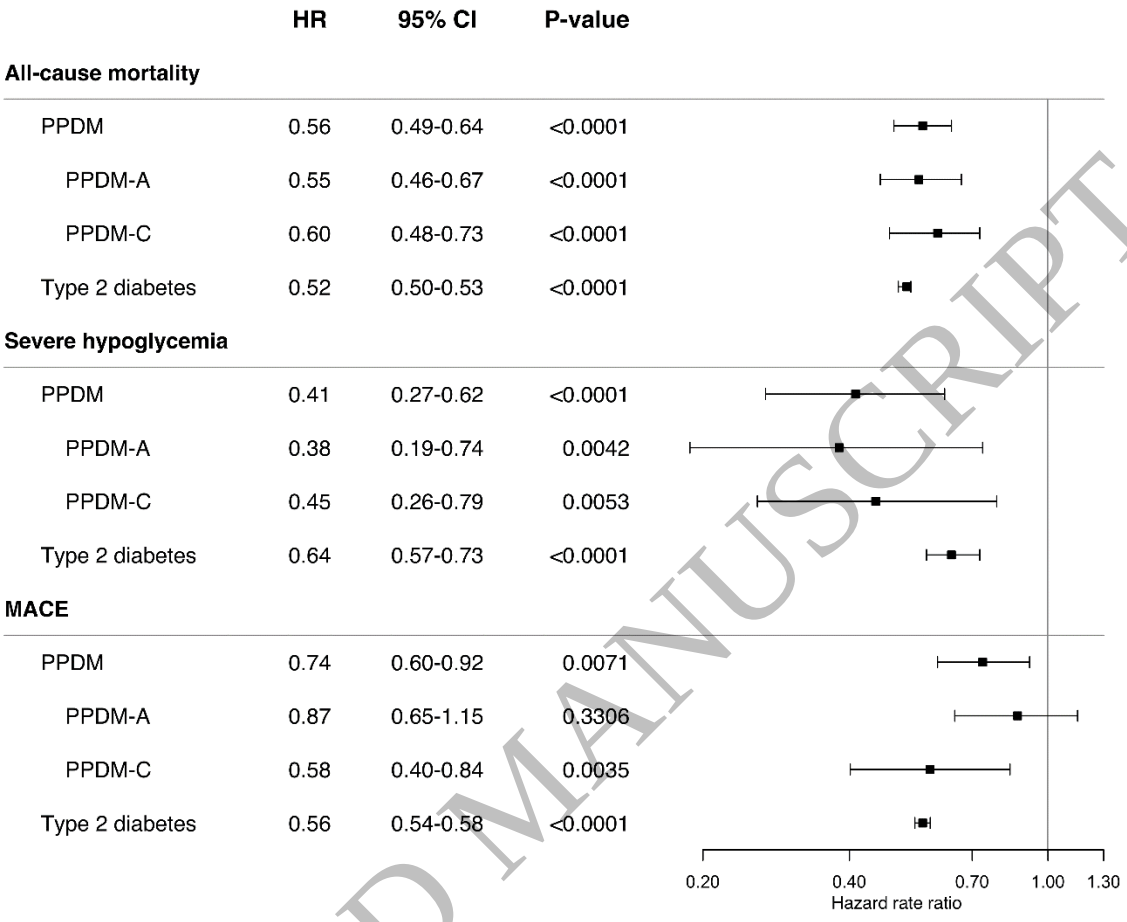


*Figure 2*
*159x130 mm (DPI)*