Association between reduced kidney function and incident hypoglycaemia in people with diabetes: The Stockholm Creatinine Measurements (SCREAM) project

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Abstract
Aim: To evaluate possible associations between estimated glomerular filtration rate (eGFR) and hypoglycaemia in adults with diabetes.

Methods: We conducted an observational study in adults with diabetes from the Stockholm Creatinine Measurement (SCREAM) project, a Swedish healthcare utilization cohort during 2007 to 2011. We evaluated diagnoses and outpatient glucose tests for incidence rate ratios (IRRs) of hypoglycaemia (overall and by severity) in outpatient care by eGFR strata using zero-inflated negative binomial regression. We identified clinical predictors through ordinal logistic regression and assessed 7-day and 30-day mortality from hypoglycaemia in relation to eGFR with Cox proportional hazard models.

Results: We identified 29,434 people with diabetes (13% with type 1 diabetes). Their mean age was 66 years, 43% were women and the median eGFR was 80 mL/min/1.73 m². During 2 years of follow-up, 1812 patients (6.2%) had hypoglycaemia registered at least once. The risk of hypoglycaemia increased linearly with lower eGFR, with an IRR of 1.2 (95% confidence interval [CI] 1.0–1.4) for eGFR 60–89 mL/min/1.73 m² and 5.8 (95% CI 3.8–9.0) for eGFR <15 mL/min/1.73 m² compared to eGFR 90 to 104 mL/min/1.73 m². This trend was observed for both mild and severe hypoglycaemia. Both 7-day and 30-day post-hypoglycaemia mortality increased with lower eGFR, peaking in those with eGFR <15 mL/min/1.73 m² (hazard ratio 21.2, 95% CI 5.1–87.9) as compared to those with eGFR 90 to 104 mL/min/1.73 m². Lower eGFR categories, type 1 diabetes, previous hypoglycaemia, liver disease, presence of diabetic complications and use of insulin and sulphonylureas increased the odds of hypoglycaemia.

Conclusion: In this large, observational study, low eGFR was strongly associated with the occurrence, severity and fatality of hypoglycaemia in people with diabetes.

Keywords
chronic kidney disease, clinical epidemiology, diabetes, hypoglycaemia
1 | INTRODUCTION

Diabetes mellitus represents a major challenge to health worldwide, with an estimated global prevalence in adults of 9.3% in 2019. Diabetes and chronic kidney disease (CKD) share risk factors and have parallel projections; approximately 25% of people with diabetes have CKD, and approximately 45% of incident cases of end-stage kidney disease in the United States and in Sweden are ascribed to diabetes nephropathy or have diabetes concomitant to other renal diseases (Swedish Renal Register 2019 report, www.snronline.se).

Hypoglycaemia is a common and potentially severe complication of diabetes treatment, and an important complication associated with glycaemic control. Hypoglycaemia may cause dizziness, seizures and loss of consciousness; and put patients at risk of cardiovascular events and death. Intense glucose-lowering therapy, although offering long-term protection against microvascular and macrovascular complications, exposes patients to hypoglycaemia risk, and has been shown to increase mortality.

People with diabetes and CKD are likely to be more susceptible to hypoglycaemia because of altered drug metabolism, drug incompatibility, autonomic neuropathy, decreased renal gluconeogenesis and insulin clearance, and multi-morbidity. However, studies of the incidence and severity of hypoglycaemia in people with diabetes and differing kidney function are few, and their results conflicting; low kidney function has been associated with hospital-requiring hypoglycaemia in elderly people with diabetes, and with overall hypoglycaemia in recently hospitalized, mainly elderly men. By contrast, a study evaluating continuous glucose measurements found no difference in hypoglycaemia occurrence between patients with and without CKD. In the present observational study of people with diabetes receiving routine care, we test the hypothesis that reduced kidney function increases the risk and severity of hypoglycaemia.

2 | MATERIALS AND METHODS

2.1 | Data sources

This is a retrospective observational study within the Stockholm Creatinine Measurement (SCREAM) project, a healthcare utilization cohort described in detail elsewhere. In brief, the SCREAM database contains laboratory test results from any resident of Stockholm having had plasma or serum creatinine measured at least once during 2006 to 2011. These laboratory tests were linked, via the unique personal identification number, to regional and national administrative databases with complete information on healthcare use, pharmacy-dispensed drugs, validated renal outcomes, diagnosis according to the International Classification of Disease 10th Revision (ICD-10) codes, vital status and other demographic data, with no loss to follow-up. The SCREAM project covers 97% of people with diabetes in our region. The regional ethical review board in Stockholm approved the study; informed patient consent was not deemed necessary since all data were de-identified at the government’s offices.

For the present study, we included adults with diabetes, with known kidney function and a recent glucose measurement (Figure S1 in Appendix S1). Participants were included if aged 18 years or older, with an outpatient diagnosis of type 1 or 2 diabetes (ICD-10 codes E10, E11, E13-E14) and with a dispensed prescription of anti-hyperglycaemic medication within 6 months from index date. Patients receiving kidney replacement therapy (transplantation or chronic dialysis) were excluded. The index date was the date of the first outpatient measurement of estimated glomerular filtration rate (eGFR) between January 2007 and December 2010. We then imposed the inclusion criterion of having at least one outpatient glucose measurement at the time of eGFR testing or within the previous year, to restrict our analysis to patients monitored for their diabetes.

2.2 | Study exposure

The study exposure was eGFR. This was calculated using measurements of plasma creatinine. We only considered creatinine measurements taken in outpatient care, and excluded implausible values (<25 or >1500 μmol/L). Creatinine was measured using the enzymatic or corrected Jaffe method. For eGFR estimations, we employed the Chronic Kidney Disease Epidemiology Collaboration formula, and we grouped the exposure into six categories of eGFR: >104; 90 to 104; 60 to 89; 30 to 59; 15 to 29; and < 15 mL/min/1.73 m². The category of eGFR 90 to 104 mL/min/1.73 m² was chosen as the referent category, based on previous studies showing minimal risks in this category, and in consideration of potential risk differences at both higher and lower GFR.

2.3 | Study covariates

Study covariates included age, sex, demographics, type 1 or 2 diabetes comorbidities, ongoing medication and laboratory values. Confounders were identified based on biological plausibility. Type 1 diabetes was defined by the presence of relevant ICD-10 diagnoses (E10) together with a recent (within 6 months from index date) insulin dispensation. Comorbidities (definitions detailed in Table S1 in Appendix S1) included diabetic complications, cardiovascular disease, cerebrovascular disease, cancer, peripheral vascular disease, chronic obstructive pulmonary disorder, hypertension, dementia, liver disease and alcoholic disorder. We also considered previous healthcare use (number of hospitalizations and outpatient consultations within the previous 12 months), as well as the number of glucose tests undertaken within the previous 12 months, as surrogate indicators of illness in general and glucose control surveillance.

Ongoing medication (definitions detailed in Table S1 in Appendix S1) was defined as a dispensed prescription within 6 months before index date, identified through the Swedish medication registry. Medications considered were antidiabetic drugs and other drugs that could affect blood glucose, and that are common in the management of CKD. Sodium-glucose co-transporter-2 inhibitors were not yet
available in the period of data collection, and dipeptidyl peptidase-4 inhibitors and glucagon-like peptide-1 receptor agonists had recently become commercially available. Laboratory values included blood glucose, glycated haemoglobin (HbA1c) and cholesterol, all of them measured in outpatient consultations. The measurement closest to index date and within 1 year prior to this date was considered the baseline measurement.

2.4 Study outcome

The study outcome was the occurrence of clinically detected hypoglycaemia during the 2 years of follow-up. Hypoglycaemia was detected through evaluation of glucose measurements in connection to an outpatient healthcare encounter (including both primary healthcare or outpatient specialist care), or through the presence of outpatient hypoglycaemia ICD-10 codes (E16.0–2, E11.6A, E10.6A, E11.0C or E10.0C). We defined hypoglycaemia as a blood glucose level <4 mmol/L, as suggested by the American Diabetes Association (ADA).6 We only considered blood glucose tests that were sampled in outpatient care and emergency units, and we also included blood glucose tests taken on the day of a hospital admission. To minimize the influence of acute illness, in-hospital measurements and outpatient measurements taken within 24 hours from a hospital discharge were excluded. For any detected low glucose test, we excluded glucose measurements during the following 7 days, as we assumed they were part of the same event or its resolution.

The severity of hypoglycaemia was subdivided into two levels, based on ADA guidelines and similarly to previous studies.5,15,27 Mild hypoglycaemia corresponded to ADA hypoglycaemia level 1 (plasma or capillary glucose 3.0 to 3.9 mmol/L, and no ICD-10 diagnosis of hypoglycaemia). Moderate-to-severe hypoglycaemia was a composite of ADA hypoglycaemia level 2 and 3 (defined by either a blood glucose <3 mmol/L, or the presence of an ICD-10 diagnosis of hypoglycaemia).

Finally, we evaluated the risk of fatal hypoglycaemia, defined as incident hypoglycaemia followed by death. We quantified 7-day and 30-day mortality following hypoglycaemia. Because of the low number of fatal events, we reduced the covariates in multivariate modelling proportionally, to avoid overfitting. Information on death was ascertained by linkage with the National Population Registry, which has no loss to follow-up. Patients were followed for 2 years, or until death, migration from the region or end of data collection (December 2011), whichever occurred first.

2.5 Statistical methods

Values are expressed as mean and SD for continuous variables with normal distribution, median (interquartile range) for non-normal distribution variables, and percentage of total for categorical variables. We first estimated the 2-year incidence proportion of hypoglycaemia across eGFR strata. We calculated incidence rate ratios (IRRs) for hypoglycaemia across eGFR stages with zero-inflated negative binomial regression (a variant of the Poisson regression that better handles over-dispersed data and that independently models excess zero counts), adjusted for demographics, comorbidities and medication. To illustrate the non-linear relationship between eGFR (as a continuous variable) and hypoglycaemia risk, we used restricted cubic splines with four degrees of freedom; this was also done to depict hypoglycaemia-associated 30-day mortality as a function of eGFR. Baseline predictors of hypoglycaemia were identified through ordinal logistic regression.

For variables with missing values, namely HbA1c (missing in 21% of patients, n = 6222) and cholesterol (31% missing, n = 9187), we performed multiple imputation (where missing values are replaced by multiple sets of simulated values, and adjustment is then made for missing value uncertainty) in Stata. Finally, Cox proportional hazards models were used to calculate the risk of fatal hypoglycaemia.

Subgroup analyses were performed to test the potential effect modification of age and sex. One underlying assumption of the zero-inflated negative binomial model is that the recurrence of the event is independent from its first occurrence. In the case of hypoglycaemia, the first event increases the likelihood of recurrence. Hence, we applied the Andersen–Gill method as a sensitivity analysis, which assumes that events are influenced by previous occurrences.28

Two-sided P values <0.05 were taken to indicate statistical significance. We did not correct for multiple comparisons. All analyses were performed using STATA Version 15 (StataCorp, College Station, Texas) and R 3.4.3 software (The R Project for Statistical Computing, Vienna, Austria).

3 RESULTS

3.1 Baseline characteristics

A total of 107 858 people had accessed healthcare and had a diagnosis of diabetes in the region of Stockholm during 2006 to 2011. After applying inclusion and exclusion criteria, a total of 29 434 individuals remained eligible for study inclusion (Figure 1 in Appendix S1).

Baseline characteristics are shown in Table 1 according to eGFR strata. The median age was 66 years and 43% were women. A total of 3959 participants (13.4%) had type 1 diabetes. Diabetic eye complications (18%) and other diabetic complications (33% of cases, including peripheral vascular complications, nephropathy, neuropathy and osteoarthritis) were relatively common. Hypertension was the most common comorbidity (55%), followed by CKD (eGFR <60 mL/min/1.73 m²; 20%) and congestive heart failure (16%). The median (interquartile range) HbA1c level was 43 (36–54) mmol/mol. Metformin was the most commonly prescribed drug (39%), followed by sulphonylureas. Use of anti-hypertensives was also common.

Across worsening eGFR categories, the prevalence of diabetic complications increased, as well as that of most comorbidities. Patients with lower eGFR categories more often had a history of hypoglycaemia episodes (by ICD-10 codes) prior to study entry. Notably, 19% of participants with eGFR <45 mL/min/1.73 m² were...
| Participant characteristics | eGFR \(<15\ mL/min/1.73\ m^2\) | 15–29 mL/min/1.73 m² | 30–44 mL/min/1.73 m² | 45–59 mL/min/1.73 m² | 60–89 mL/min/1.73 m² | 90–104 mL/min/1.73 m² | >104 mL/min/1.73 m² |
|-----------------------------|-----------------|------------------|------------------|-----------------|-----------------|-----------------|-----------------|
| Number                      | 29 434          | 141              | 663              | 1860            | 3320            | 12 479          | 8310            | 3835            |
| Median (IQR) age, years     | 66 (57–76)      | 72 (62–83)       | 79 (71–85)       | 80 (73–85)      | 77 (70–83)      | 70 (63–77)      | 61 (55–66)      | 47 (40–54)      |
| Women, %                    | 43              | 40               | 52               | 51              | 51              | 44              | 37              | 40              |
| Diabetic eye complications (%) | 18              | 50               | 35               | 27              | 23              | 17              | 14              | 14              |
| Other diabetic complications, % | 33              | 82               | 65               | 55              | 43              | 32              | 27              | 22              |
| Previous hypoglycaemia, %   | 2.6             | 11.4             | 7.5              | 5.6             | 3.5             | 2.3             | 1.6             | 2.6             |
| Type 1 diabetes, n (%)      | 3959 (13.4)     | 36 (25)          | 157 (24)         | 285 (15.9)      | 402 (12.7)      | 1339 (11)       | 881 (11.5)      | 859 (22)        |
| Comorbidities, %            |                 |                  |                  |                 |                 |                 |                 |                 |
| Ischaemic heart disease     | 13              | 25               | 29               | 27              | 21              | 13              | 8.8             | 4.4             |
| Congestive heart failure    | 16              | 37               | 55               | 47              | 33              | 16              | 7.2             | 3.3             |
| Cerebrovascular disease     | 7.4             | 23               | 19               | 20              | 13              | 7.0             | 3.9             | 2.0             |
| Hypertension                | 55              | 85               | 75               | 76              | 69              | 58              | 49              | 33              |
| Peripheral vascular disease | 13              | 25               | 26               | 25              | 20              | 14              | 8.5             | 4.3             |
| Chronic obstructive pulmonary disease | 11          | 14               | 18               | 16              | 13              | 11              | 9.4             | 7.9             |
| Cancer                      | 11              | 16               | 15               | 16              | 15              | 12              | 7.5             | 3.5             |
| Dementia                    | 2.4             | 5.0              | 7.1              | 5.1             | 4.8             | 2.9             | 0.8             | 0.2             |
| Liver disease               | 1.1             | 1.4              | 1.2              | 1.1             | 0.9             | 0.9             | 1.1             | 1.2             |
| Alcohol disorders           | 4.8             | 4.3              | 2.8              | 2.6             | 2.9             | 3.4             | 6.4             | 8.8             |
| Laboratory values           |                 |                  |                  |                 |                 |                 |                 |                 |
| Mean (SD) eGFR mL/min/1.73 m² | 80 (23)         | 11 (2.5)         | 24 (4.1)         | 38 (4.3)        | 53 (4.3)        | 77 (8.6)        | 97 (3.9)        | 113 (8.1)       |
| Median (IQR) HbA1c, mmol/mol | 42 (36–53)      | 40 (34–51)       | 45 (37–57)       | 44 (37–55)      | 43 (37–53)      | 43 (36–51)      | 42 (34–53)      | 45 (36–61)      |
| Mean (SD) cholesterol, mmol/L | 4.9 (1.1)       | 4.5 (1.2)        | 4.8 (1.2)        | 4.8 (1.1)       | 4.8 (1.1)       | 4.8 (1.0)       | 5.0 (1.2)       | 5.1 (1.2)       |
| Medication                  |                 |                  |                  |                 |                 |                 |                 |                 |
| ACE inhibitors/ARBs         | 52              | 72               | 73               | 68              | 64              | 54              | 47              | 30              |
| Statins                     | 45              | 58               | 51               | 51              | 52              | 48              | 45              | 28              |
| Aspirin                     | 39              | 52               | 57               | 56              | 52              | 42              | 33              | 17              |
| Participant characteristics   | Overall | eGFR     | 15–29 mL/min/1.73 m² | 30–44 mL/min/1.73 m² | 45–59 mL/min/1.73 m² | 60–89 mL/min/1.73 m² | 90–104 mL/min/1.73 m² | >104 mL/min/1.73 m² |
|------------------------------|---------|----------|----------------------|----------------------|----------------------|----------------------|----------------------|---------------------|
| Sulphonylureas               | 25      | 11       | 26                   | 33                   | 34                   | 27                   | 21                   | 14                  |
| Metformin                    | 39      | 2.8      | 12                   | 23                   | 34                   | 41                   | 46                   | 39                  |
| Thiazolidendiones            | 3.6     | 0.7      | 1.7                  | 2.5                  | 2.9                  | 3.4                  | 4.7                  | 3.4                 |
| α-glucosidase inhibitors     | 0.7     | 0.0      | 0.9                  | 0.8                  | 0.7                  | 0.7                  | 0.8                  | 0.6                 |
| Glinides                     | 2.6     | 5.7      | 2.0                  | 3.4                  | 2.6                  | 2.8                  | 2.8                  | 1.5                 |
| Insulin, meal-time           | 14      | 28       | 21                   | 14                   | 13                   | 11                   | 13                   | 24                  |
| Insulin, intermediate-acting | 14      | 22       | 22                   | 19                   | 16                   | 13                   | 13                   | 15                  |
| Insulin, premix              | 12      | 28       | 33                   | 24                   | 18                   | 11                   | 8.3                  | 8.3                 |
| Insulin, long-acting         | 9.6     | 21       | 13                   | 9.6                  | 8.5                  | 7.6                  | 9.2                  | 17                  |
| β-blockers                   | 42      | 67       | 65                   | 62                   | 57                   | 45                   | 35                   | 21                  |
| Calcium channel blockers     | 22      | 55       | 36                   | 28                   | 28                   | 25                   | 19                   | 10                  |

Healthcare consumption in the previous year

| Metric                               | Overall | <15 mL/min/1.73 m² | 15–29 mL/min/1.73 m² | 30–44 mL/min/1.73 m² | 45–59 mL/min/1.73 m² | 60–89 mL/min/1.73 m² | 90–104 mL/min/1.73 m² | >104 mL/min/1.73 m² |
|--------------------------------------|---------|-------------------|----------------------|----------------------|----------------------|----------------------|----------------------|---------------------|
| Median (IQR) number of blood glucose tests | 2 (2–4) | 2 (2–4)           | 2 (2–4)             | 2 (2–3)             | 2 (2–3)             | 2 (2–3)             | 2 (2–3)             | 2 (1–3)             |
| Median (IQR) number of outpatient visits | 2 (1–5) | 8 (3–15)         | 4 (1–8)              | 3 (1–6)             | 2 (1–5)             | 2 (0–5)             | 2 (0–5)             | 2 (1–6)             |
| Number of primary care visits        | 2 (0–4) | 1 (0–3)           | 2 (0–4)              | 2 (1–4)             | 2 (0–4)             | 2 (0–4)             | 1 (0–3)             | 1 (0–3)             |
| Median (IQR) number of hospitalizations | 1 (0–3) | 1 (0–3)           | 1 (0–2)              | 0 (0–1)             | 0 (0–1)             | 0 (0–1)             | 0 (0–1)             | 0 (0–1)             |

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; IQR, interquartile range.
TABLE 2 Crude 2-year incidence proportion (cumulative incidence) of hypoglycaemia (%) across estimated glomerular filtration rate categories

| eGFR            | Hypoglycaemia (95% CI) | Mild hypoglycaemia (95% CI) | Moderate–severe hypoglycaemia (95% CI) |
|-----------------|------------------------|-------------------------------|----------------------------------------|
| >104 mL/min/1.73 m² | 4.9 (4.2–5.6)          | 2.4 (2.0–3.0)                 | 2.4 (2.0–3.0)                          |
| 90–104 mL/min/1.73 m² | 3.9 (3.5–4.4)          | 2.2 (1.9–2.6)                 | 1.7 (1.5–2.0)                          |
| 60–89 mL/min/1.73 m² | 5.5 (5.1–5.9)          | 3.1 (2.8–3.4)                 | 2.4 (2.1–2.6)                          |
| 45–59 mL/min/1.73 m² | 8.5 (7.6–9.5)          | 4.7 (4.0–5.5)                 | 3.8 (3.2–4.5)                          |
| 30–44 mL/min/1.73 m² | 12 (11–14)             | 6.1 (5.1–7.3)                 | 6.4 (5.3–7.6)                          |
| 15–29 mL/min/1.73 m² | 18 (16–22)             | 9.5 (7.5–12)                  | 8.8 (6.8–11)                           |
| <15 mL/min/1.73 m²  | 32 (25–40)             | 22 (16–30)                    | 9.9 (6.0–16)                           |

Abbreviation: eGFR, estimated glomerular filtration rate. Mild hypoglycaemia: blood glucose 3.0–3.9 mmol/L and no International Classification of Diseases, tenth revision (ICD-10) diagnosis of hypoglycaemia. Moderate-to-severe hypoglycaemia: blood glucose <3.0 mmol/L or relevant ICD-10 code.

TABLE 3 Incidence rate ratios for hypoglycaemia (overall and by severity) across estimated glomerular filtration rate categories

| eGFR         | Unspecified hypoglycaemia | Mild hypoglycaemia | Moderate/severe hypoglycaemia |
|--------------|---------------------------|--------------------|-------------------------------|
|              | Age-, sex-adjusted IRR (95% CI) | Fully adjusted IRR (95% CI) | P   | Age-, sex-adjusted IRR (95% CI) | Fully adjusted IRR (95% CI) | P   |
| >104 mL/min/1.73 m² | 1.4 (1.1–1.7)             | 1.1 (0.9–1.3)       | .5  | 1.1 (0.9–1.4)               | 1.0 (0.8–1.3)       | .8  |
| 90–104 mL/min/1.73 m² | 1.4 (1.2–1.6)             | 1.2 (1.0–1.4)       | .03 | 1.4 (1.2–1.7)              | 1.3 (1.1–1.5)       | .02 |
| 60–89 mL/min/1.73 m² | 2.1 (1.7–2.5)             | 1.5 (1.2–1.8)       | <.01 | 2.1 (1.6–2.6)              | 1.5 (1.2–1.9)       | <.01 |
| 45–59 mL/min/1.73 m² | 3.6 (2.9–4.5)             | 2.1 (1.7–2.7)       | <.01 | 3.3 (2.5–4.3)              | 2.0 (1.5–2.6)       | <.01 |
| 30–44 mL/min/1.73 m² | 6.0 (4.5–8.0)             | 2.6 (1.9–3.4)       | <.01 | 5.8 (4.2–8.2)              | 3.2 (2.3–4.5)       | <.01 |
| 15–29 mL/min/1.73 m² | 18 (11–31)                | 9.5 (5.7–16)        | <.01 | 11 (5.7–22)                | 4.2 (2.4–7.6)       | <.01 |

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; IRR, incidence rate ratio. Fully adjusted model considered age, sex, diabetes type, diabetic eye complications, other diabetic complications, previous hypoglycaemia history, comorbidities (hypertension, ischaemic heart disease, congestive heart failure, cerebrovascular disease, peripheral vascular disease, cancer, dementia, liver disease, chronic obstructive pulmonary disease, alcoholic disease), ongoing medication (angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, statins, aspirin, metformin, sulphonylureas, thiazolidinediones, oral antidiabetics, insulin, β-blockers, calcium channel blockers), glycated haemoglobin and cholesterol levels, and previous healthcare use (number of primary care visits, outpatient visits, hospitalizations and glucose measurements).

receiving metformin, which would be an off-label use at that time (before the 2016 European Medicines Agency recommendation to use metformin for type 2 diabetes with eGFR down to 30 mL/min/1.73 m²).²⁹ HbA1c did not vary meaningfully across eGFR strata.

3.2 eGFR and risk of hypoglycaemia, overall and by severity

During 2 years of follow-up (median 731 days), all participants had glucose tested in connection to a healthcare consultation at least once. A total of 2397 hypoglycaemia episodes were detected in 1812 individuals, 6.2% of the study population. The crude incidence proportion increased across lower eGFR strata (Table 2).

Compared to participants with eGFR 90 to 104 mL/min/1.73 m², the IRR for hypoglycaemia steadily increased with lower eGFR (Table 3, Figure 1), peaking in participants with eGFR <15 mL/min/1.73 m²: IRR 5.8 (95% confidence interval [CI] 3.8–9.0). This increased hypoglycaemia risk was similar in direction and magnitude for both mild and moderate/severe hypoglycaemia. Because medications may be viewed as mediators between diseases and outcomes, a more simplified model not including ongoing medication was used, and similar results were observed (Table S2 in Appendix S1).

3.3 eGFR and risk of fatal hypoglycaemia

A total of 77 participants died within 30 days, and 26 within 7 days of incident hypoglycaemia. Compared to participants with eGFR 90 to
104 mL/min/1.73 m², the risk of fatal hypoglycaemia increased with lower eGFR strata (Table 4 and Table S3).

3.4 | Sensitivity analyses

Subgroup analyses showed no significant effect modification by age strata or sex (Table S4 in Appendix S1). Sensitivity analyses applying the Andersen–Gill extension of the Cox proportional hazards model showed results consistent with our main analysis (Table S5 in Appendix S1). Finally, exclusion of people with type 1 diabetes did not modify our main conclusions (Table S6 in Appendix S1).

3.5 | Baseline predictors of hypoglycaemia occurrence

Table 5 presents odds ratios for incident hypoglycaemia in relation to baseline characteristics. Lower eGFR strata, presence of diabetic complications, type 1 diabetes, previously documented hypoglycaemia, and type 1 diabetes, hypoglycaemia-associated 30-day mortality. The model was adjusted for age, sex, diabetes type, diabetic eye complications, other diabetic complications, previous hypoglycaemia history, comorbidities (hypertension, ischaemic heart disease, congestive heart failure, cerebrovascular disease, peripheral vascular disease, cancer, dementia, liver disease, chronic obstructive pulmonary disease, alcoholic disease), ongoing medication (angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, statins, aspirin, metformin, sulphonylureas, thiazolidinediones, other oral antidiabetic agents, insulin, β-blockers, calcium channel blockers), glycated haemoglobin and cholesterol levels, and previous healthcare use (number of primary care visits, outpatient visits, hospitalizations and glucose measurements). For graphical representation, curves were truncated at eGFR 100 mL/min/1.73 m².
**Table 4** Hazard ratio for death within 30 days of incident hypoglycaemia, according to estimated glomerular filtration rate

| eGFR                  | Sex- and age-adjusted HR (95% CI) | P    | Multivariable-adjusted | P |
|-----------------------|-----------------------------------|------|------------------------|---|
| >104 mL/min/1.73 m²   | 2.6 (0.7–9.6)                     | 0.1  | 2.7 (0.7–9.4)          | 0.1 |
| 90–104 mL/min/1.73 m² | 1 (reference)                     |      |                        |    |
| 60–89 mL/min/1.73 m²  | 1.2 (0.5–3.1)                     | 0.7  | 1.0 (0.4–2.7)          | 0.9 |
| 45–59 mL/min/1.73 m²  | 3.4 (1.2–9.4)                     | 0.2  | 2.6 (0.9–7.2)          | 0.1 |
| 30–44 mL/min/1.73 m²  | 4.5 (1.6–13)                      | 0.005| 3.1 (1.1–9.0)          | 0.06|
| 15–29 mL/min/1.73 m²  | 13.2 (4.5–38.4)                   | <0.001|8.1 (2.8–23)           | <0.001|
| <15 mL/min/1.73 m²    | 21.2 (5.1–87.9)                   | <0.001|11 (2.7–47)            | 0.001|

aBecause of the low number of events, we considered a simplified multivariable model adjusted for age, sex, diabetes type and diabetic complications.

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio.

**Table 5** Predictors of hypoglycaemia, presented as odds ratios with 95% confidence intervals

|                      | Any hypoglycaemia | Mild hypoglycaemia | Moderate to severe hypoglycaemia |
|----------------------|-------------------|--------------------|---------------------------------|
| General characteristics |                   |                    |                                 |
| Female sex           | 1.0 (0.9–1.1)     | 0.9 (0.8–1.0)      | 1.0 (0.9–1.2)                   |
| Age (per year)       | 1.02 (1.01–1.02)  | 1.01 (1.01–1.02)   | 1.02 (1.01–1.02)                |
| eGFR (90–104 = reference) |                 |                    |                                 |
| >104 mL/min/1.73 m²  | 1.2 (1.0–1.5)     | 1.2 (0.9–1.5)      | 1.4 (1.1–1.8)                   |
| 60–89 mL/min/1.73 m² | 1.4 (1.2–1.6)     | 1.4 (1.2–1.7)      | 1.3 (1.1–1.6)                   |
| 45–59 mL/min/1.73 m² | 2.3 (1.9–2.7)     | 2.1 (1.7–2.7)      | 2.2 (1.7–2.8)                   |
| 30–44 mL/min/1.73 m² | 3.5 (2.9–4.2)     | 3.0 (2.4–3.9)      | 3.8 (3.0–4.8)                   |
| 15–29 mL/min/1.73 m² | 5.5 (4.3–6.9)     | 5.2 (3.9–7.0)      | 5.7 (4.2–7.7)                   |
| <15 mL/min/1.73 m²   | 10.4 (7.2–15)     | 13.6 (9.0–20.5)    | 10.1 (6.3–16.2)                 |
| Complications and comorbidities |         |                    |                                 |
| Type 1 diabetes      | 3.1 (2.8–3.4)     | 2.4 (3.4–3.5)      | 3.6 (3.2–4.2)                   |
| Diabetic eye complications | 2.2 (2.0-2.5) | 1.8 (1.6–2.1)      | 2.7 (2.4–3.2)                   |
| Other diabetic complications | 2.4 (2-2.6)  | 2.1 (1.9–2.4)      | 2.6 (2.3–3.0)                   |
| Previous hypoglycaemia | 5.2 (4.3–6.1) | 3.3 (2.5–4.2)      | 6.7 (5.4–8.3)                   |
| Congestive heart failure | 2.0 (1.8–2.3) | 1.9 (1.7–2.2)      | 2.1 (1.8–2.4)                   |
| Ischaemic heart disease | 1.6 (1.4–1.8) | 1.6 (1.4–1.9)      | 1.7 (1.4–2.0)                   |
| Cerebrovascular disease | 2.2 (1.9–2.6) | 2.2 (1.9–2.7)      | 2.2 (1.9–2.7)                   |
| Dementia              | 1.6 (1.3–2.1)     | 1.2 (0.8–1.7)      | 2.2 (1.6–3.0)                   |
| Liver disease         | 2.9 (2.1–3.9)     | 3.2 (2.2–4.8)      | 2.7 (1.7–4.2)                   |
| Alcoholic disorder    | 1.9 (1.6–2.3)     | 1.5 (1.1–1.9)      | 2.4 (1.9–3.0)                   |
| Medication            |                   |                    |                                 |
| Metformin             | 0.5 (0.4–0.5)     | 0.5 (0.5–0.6)      | 0.4 (0.3–0.5)                   |
| Sulphonylureas        | 1.3 (1.1–1.4)     | 1.3 (1.1–1.4)      | 1.2 (1.1–1.4)                   |
| α-glucosidase inhibitors | 0.7 (0.4–1.3) | 0.7 (0.3–1.6)      | 0.9 (0.4–2.0)                   |
| Thiazolidendiones     | 0.5 (0.4–0.7)     | 0.6 (0.4–0.9)      | 0.4 (0.2–0.7)                   |
| Insulin, unspecified  | 9.8 (1.7–55)      | 15.7 (2.8–88)      | 10.2 (1.0–96)                   |
| Insulin, meal time    | 2.9 (2.6–3.2)     | 2.5 (2.2–2.9)      | 3.1 (2.7–3.6)                   |
| Insulin, intermediate | 1.8 (1.6–2.0)     | 2.0 (1.8–2.3)      | 1.5 (1.3–1.8)                   |
| Insulin, premixed     | 2.8 (2.5–3.1)     | 2.4 (2.1–2.8)      | 3.1 (2.7–3.7)                   |
| Insulin, long-acting  | 2.9 (2.5–3.2)     | 2.6 (2.4–3.0)      | 3.0 (2.6–3.6)                   |

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate.
Statistical significance (P < 0.05) was observed for odd ratios whose 95% CI did not cross one.
(ICD-10 diagnosis), congestive heart failure, cerebrovascular disease, liver disease and alcohol disorders were associated with the odds of hypoglycaemia. Among ongoing drug regimens, the use of insulin and sulphonylureas was associated with higher hypoglycaemia odds ratios, whereas metformin and thiazolidenediones were associated with lower odds. Previous hypoglycaemia, dementia, alcohol disorder and the use of fast-acting insulin were more strongly associated with the odds of moderate-to-severe hypoglycaemia than of mild hypoglycaemia.

4 | DISCUSSION

In this large observational analysis of almost 30,000 people with diabetes (both type 1 and 2) and known kidney function, we observe a consistent and strong inverse association between eGFR and the risk of hypoglycaemia. Associations were already observed at mild eGFR reductions, such as eGFR 60 to 89 mL/min/1.73 m².

This analysis expands and complements prior evidence on increased susceptibility for hypoglycaemia in people with low eGFR.16,17,20,21,30 For example, Moen et al.16 observed that among male patients hospitalized for a cardiovascular cause, and treated at the Veterans Health Administration in the United States, an eGFR <60 mL/min/1.73 m² conferred a higher risk of detected hypoglycaemia (glucose <70 mg/dL). Hodge et al.21 reported a higher 3-year incidence rate of hospital encounters for hypoglycaemia (emergency department or inpatient encounter) across elderly Canadian healthcare users with low eGFR. We have expanded their observations to unselected people with diabetes of all adult ages. The use of outpatient glucose measurements performed in our healthcare system (including primary and outpatient specialist care) improves precision and allows us to study mild as well as moderate/severe events. However, we acknowledge that we can only evaluate them to the extent that hypoglycaemia episodes are detected in routine clinical practice. Our results differ from those of an observational case–control study of people with type 2 diabetes undergoing continuous glucose monitoring,22 in which no difference in hypoglycaemia incidence was observed between patients with eGFR below versus above 60 mL/min/1.73 m². Reasons for this discrepancy may include potential patient selection bias (with patients more engaged in their diabetes control willing to participate), a relatively small number of participants (81 cases with CKD), and limited measurement time (12 days). Our results also differ from those of a secondary analysis of the DEVOTE-1 trial,17 where there was a nonsignificant trend towards higher rates of severe hypoglycaemia with lower eGFR categories. The careful, controlled nature of the trial protocol (as compared with routine care) and the fact that people with eGFR <30 mL/min were excluded at screening21,32 may have obscured these associations.

We observed that the incidence of mild, moderate/severe as well as fatal hypoglycaemia increases with lower eGFR, which again accords with and expands previous reports of an association between hypoglycaemia and the risk of hospitalization and death among people with diabetes and eGFR <60 mL/min/1.73 m² or transitioning to dialysis.16,33 We also note that those at the higher end of the eGFR categories in our population (≥105 mL/min) were also at somewhat increased hypoglycaemia risk. On the one hand, the high end of eGFR values might represent inaccurate estimations of true GFR caused by low serum creatinine, which usually accompanies conditions of reduced muscle mass or chronic illness.34 On the other hand, higher eGFR is observed in hyperfiltration, and glomerular hyperfiltration is a hallmark of renal dysfunction in diabetes and obesity.35,36

Our analysis identified numerous baseline predictors of hypoglycaemia, which probably represent a non-specific relationship between hypoglycaemia and poor health.37 In accordance with previous studies,27,38 we observed a higher incidence of hypoglycaemia among the elderly. Some comorbidities, such as liver and cerebrovascular disease, also emerged as multivariable predictors. Whereas the use of insulin and sulphonylureas was associated with a higher hypoglycaemia risk, metformin and thiazolidenediones (glitazones) conveyed a lower risk, which is consistent with the pharmacological profile of these medications.39–41 A history of severe hypoglycaemia and a low HbA1c level have emerged as important predictors of severe hypoglycaemia in type 1 diabetes.42 In the present study, higher HbA1c was associated with a higher risk of hypoglycaemia, which is supported by some,15,37,43 but not all12,44 previous evidence. Overall, the observed predictors confirm previous work18,30,43–46 and we believe lend credibility to our findings.

The possible reasons for the increased hypoglycaemia risk in people with low eGFR are many, starting with reduced gluconeogenesis in the kidney and lower insulin clearance with subsequent impaired glucose counter-regulation, resulting in higher glucose variability; these reasons are, mainly, a direct consequence of reduced kidney mass in the failing kidneys.47 Inability to metabolize anti-hyperglycaemic medications, presence of malnutrition and muscle-wasting (reducing glycogen stores)19,48 may further contribute to hypoglycaemia in CKD. This said, and because reduced kidney function accompanies multi-morbidity in general, it is also possible that the associations observed simply reflect underlying disease or duration of diabetes and insulin use.3,49

Regardless of whether the associations are causal or not, the findings of this study have potential clinical implications. Despite current recommendations from ADA to assess urinary albumin excretion and eGFR at least yearly in people with type 2 diabetes,50 evidence suggests that routine eGFR monitoring in these patients is often suboptimal.51,52 The demonstration of an association between hypoglycaemia and eGFR in our study may increase awareness, testing and monitoring of eGFR in these patients. At the same time, our listing of hypoglycaemia predictors serves to identify patient groups who may benefit from discussions on hypoglycaemia risk management,33 and for whom novel treatment choices with minimal hypoglycaemia risk should be encouraged.

This study has limitations, including the fact that all definitions of hypoglycaemia (self-reported, hospital requiring, at-home or in-hospital monitored glucose levels) have shortcomings. ICD codes are imprecise and may reflect several of these definitions (patient reported, measured glucose, clinical presentation). In addition, we did not have information on patients’ own glucose monitoring or ambulatory measurements, and ambulatory glucose measurements were
often capillary, which may, in comparison to venous samples, overestimate glucose levels, especially in the lower range.\textsuperscript{54} This is likely to have led to an underestimation of the true hypoglycaemia occurrence. However, such detection bias is applicable to all patients regardless of their eGFR and is unlikely to invalidate our findings. GFR estimations are inherently imprecise, and are subject to non-renal factors for which we were not able to account. To reduce the influence of acute illness, we excluded in-hospital values. However, aiming to identify hospital-requiring hypoglycaemia events, we included glucose measurements at hospital admission, which may have introduced bias by acute illness. Albuminuria may affect hypoglycaemia risk,\textsuperscript{30} but is less often measured, and we did not have enough measurements to evaluate this association. Our findings are framed within a Swedish population during 2006 to 2011. Extrapolation to other regions, ethnicities and time periods should be done with caution. Finally, we acknowledge the lack of unmeasured confounding, including diabetes duration, body mass index, concurrent infections and lifestyle factors such as diet, skipped meals and exercise.

In conclusion, this study shows that even mild reductions in kidney function are associated with the incidence and severity of hypoglycaemia in people with diabetes. The study underlines the need for greater provider awareness and regular monitoring of kidney function in patients with diabetes, in accordance with current ADA recommendations.

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CONFLICTS OF INTEREST

B.L. is employed by Baxter Healthcare Corporation. None of the other authors declare any conflict of interest.

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SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section at the end of this article.

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