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# Association of continuous subcutaneous insulin therapy and diabetic retinopathy in type 1 diabetes: A national cohort study

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ABSTRACT

*Aim:* This study aimed to investigate the short-and long-term effect on diabetic retinopathy (DR) in individuals with type 1 diabetes treated with continuous subcutaneous insulin injections (CSII) compared to those using multiple daily injections (MDI).

*Methods:* We conducted a register-based matched cohort study utilizing data from the Danish Registry of Diabetic Retinopathy as well as several other national Danish health registers. Our cohort consisted of all individuals with type 1 diabetes who attended the Danish screening program for DR from 2013 to 2022. We included individuals registered with CSII treatment, and compared them to individuals using MDI, matched by age, sex, and DR level. Cox regression analysis was performed to evaluate the outcomes.

*Results:* The study included 674 individuals treated with CSII and 2006 matched MDI users. In our cohort 53.4 % were female and median age was 36 (IQR 27–47). Average follow-up risk-time was 4.8 years. There was no difference in the risk of DR worsening between the CSII group and MDI group (HR 1.05 [95%CI 0.91; 1.22], $p = 0.49$). However, an increased risk of focal photocoagulation was observed in the CSII group (HR 2.40 [95%CI 1.11; 5.19], $p = 0.03$).

*Conclusions:* Our findings indicate that CSII treatment does not confer a significant difference in the overall short- and long-term risk of DR worsening or ocular intervention compared to MDI treatment. These results provide insights into the DR outcomes of CSII treatment in individuals with type 1 diabetes.

## 1. Introduction

Diabetic retinopathy (DR) is the most prevalent microvascular complication in diabetes, affecting up to 77 % of individuals with type 1 diabetes.[1] The pathophysiology of DR involves several interrelated mechanisms; hyperglycemia leads to the accumulation of sorbitol and the formation of advanced glycation end products (AGEs), which cause oxidative stress and inflammation. These processes result in endothelial dysfunction and breakdown of the blood-retinal barrier, leading to increased vascular permeability and capillary occlusion. Consequently, ischemia and hypoxia in the retina stimulate the production of vascular endothelial growth factor (VEGF), promoting neovascularization and

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further exacerbating retinal damage. Other contributing risk factors include hypertension, dyslipidemia, and genetic predisposition, which are also relevant in regards to progression of DR.[2] These pathological changes manifest as microaneurysms, hemorrhages, and macular edema, progressing from non-proliferative to proliferative stages of DR, potentially leading to severe vision loss and blindness.[3] The Diabetes Control and Complications Trial (DCCT) was a landmark study that demonstrated improved glucose control slows the onset and progression of DR.[4] This established the critical role of glycemic control in managing DR outcomes. Additionally, the follow-up study, Epidemiology of Diabetes Interventions and Complications (EDIC), confirmed the long-term benefits of tight glycemic control on DR.[5]

Continuous subcutaneous insulin infusion (CSII), also known as insulin pumps, has become increasingly popular amongst patients with type 1 diabetes. Several studies report that CSII contributes to optimized glycemic stability, proving to be beneficial or neutral regarding DR development.[6,7] CSII involves the constant delivery of fast-acting insulin through a subcutaneous tube linked to a cartridge, guaranteeing a consistent stream of insulin (basal rate) along with mealtime boluses that the user can modify depending on dietary intake.[8] However, the relationship between CSII and DR is complex. Rapid glucose lowering has been associated with worsening of retinopathy.[9] This phenomenon, known as early or transient worsening of DR, can also occur when transitioning patients with type 1 diabetes from multiple daily injections (MDI) to CSII.[9] This highlights the need to better understand the implications of different insulin delivery methods on DR. Recent studies have addressed this gap and demonstrated the benefits of CSII in maintaining stable glycemic control[10] as well as an analysis of the long-term effects of continuous glucose monitoring (CGM) on DR progression.[11] Recent advancements in these hybrid-closed loop systems, which combine insulin pumps with CGM have shown promise in further improving glycemic control and thus reducing DR risk.[12]

Despite the promising benefits of CSII treatment, the latest study examining the prevalence of CSII treatment in a specific Danish geographical region showed that only 21 % of all individuals with type 1 diabetes were treated with CSII.[13] This number roughly equates to prevalence rates in 2010 in Norway, Austria, the Netherlands, and Switzerland,[14] and might be higher today. CSII treatment has been sparsely examined in a Danish setting, and the studies that have evaluated the treatment were primarily older and had small sample sizes. Thus, larger, population-based studies are needed.

In Denmark, national registers provide a unique opportunity to examine diseases, treatments, and biochemical markers on an individualized level for the whole population. This allows for an extensive examination of CSII and DR in a nationwide setting. In this study, we will investigate the development of DR (regression, incidence, and progression) and the need for ocular intervention in individuals affected by type 1 diabetes using CSII, compared to individuals using MDI.

## 2. Research design and methods

We performed a register-based matched cohort study with data from Danish national registers. Our cohort was defined by The Danish Registry of Diabetic Retinopathy (DiaBase),[15] a national Danish clinical quality database, which holds data from all screenings performed in the Danish screening program for DR from its origin in 2013. Data is reported to the database by the screening ophthalmologist who is obligated to do so. We incorporated data from various other Danish registries; The Danish National Patient Register[16] provided information on diagnostic- and procedure-codes for in- and out-patient treatments, The National Prescription Registry[17] provided information on all prescribed and dispensed medications, The Clinical Laboratory information Register[18] added nationwide information on biochemical measurements and lastly The Danish Civil Registration System[19] provided data linkage throughout all mentioned registries by the use of the unique identification number (CPR number) given to all Danish inhabitants, as well as provided basic information on age, sex and marital status. The registers, used in this study, have been thoroughly described earlier.[20]

### 2.1. Participants

As cases (CSII group), we included individuals identified in DiaBase with type 1 diabetes, above the age of 18 at index date, that had a minimum of two registrations of either ICD-10 procedure code for CSII (BBHF02*) or insulin types used solely for CSII treatment from 2013 to 2022. Individuals who were only registered with procedure codes for CSII but did not have any relevant insulin treatment were excluded, except if the procedure codes were registered 2022. In such cases, initial medication could be administered directly to the patient with the pump in the hospital, and might not yet be prescribed. Index date was set as nearest screening date in DiaBase prior to first registration of either CSII treatment or medication. Individuals using CSII were matched 1:3 with individuals using MDI by age, sex and DR level at index date. Controls (MDI group) were selected amongst the remaining DiaBase population with type 1 diabetes and sampled with replacements. Individuals with a history of CSII prior to index date were excluded from both CSII and MDI groups.

### 2.2. Outcomes

Our main outcomes were DR worsening (incident DR [DR level 0 at index date and level 1–4 at follow up] and/or progression [≥ two-step progression or progression to PDR]) or regression (≥ two-step) in at least one eye, quantified at short- (screening date closest to six months after initiation of CSII treatment) and long-term (at the last available screening date). As a secondary outcome, we examined the need for ocular intervention (vitrectomy, panretinal- or focal laser treatment or intravitreal anti VEGF injection) during follow up. We also examined changes in biochemical measurements amongst cases and controls from index date to 3 years post CSII. HbA1c values were analyzed for the total follow up period for both cases and controls.

### 2.3. Covariates

We extracted information on screening dates and level of DR at each screening (ICDR scale,[14] 0–4 [0 = no DR, 1 = mild non proliferative DR (NPDR), 2 = moderate NPDR, 3 = severe NPDR and 4 = proliferative DR (PDR)]) from DiaBase. We extracted age, sex (female or male) and marital status (married/cohabitating, single or divorced) from The Danish Civil Registration System. The National Patient register provided information on CSII treatment (BHF002) as well as the ocular interventions; vitrectomy [(KCKD65 and H334B) or (KCKD65 and H431 and H36*)], intravitreal anti VEGF injection [(BCHY8A or KCKD05B) and not (H34* [occlusion of retinal vessels] or H353* [age related macular degeneration]) within 6 months prior to anti VEGF injection], panretinal [KCKC15 and not H34* within 6 months prior to anti VEGF injection] and focal photocoagulation [KCKC10 and H36*]) as well as systemic illnesses used to calculate a modified (excluding diabetes) Charlson Comorbidity Index score (CCI) 5 years prior to index date (0 [low], 1 [moderate low], 2 [moderate high] and ≥ 3 [high]). From The Clinical Laboratory information Register we collected information on laboratory values for measurements of hemoglobin A1c (HbA1c [% (mmol/mol)]), plasma creatinine (P-crea [μmol/L]), albumin/creatinine ratio in urine (uACR [mg/g]), estimated glomerular filtration rate (eGFR [mL/min/1.73 $m^2$]), low density lipoprotein cholesterol (LDL [mmol/L]), total cholesterol (mmol/L), high density lipoprotein cholesterol (HDL [mmol/L] and triacylglyceroles (TG [mmol/L]). Finally, we extracted information on prescribed and dispensed insulin used in CSII treatment from The Danish National Prescription Registry. To distinguish patients according to type of diabetes (type 1 and 2 diabetes), we examined patients' diagnosis- and pharmaceutical codes from The Danish National Patient Register and The Danish National

Prescription Registry and separated them using an endocrinologist recommended algorithm (see Appendix 1).

## 3. Statistical methods

Data are presented descriptively with medians and interquartile ranges (IQR) or counts and percentages. Statistical significance was defined as $p$-values $<0.05$ and confidence intervals excluding one. In Table 1, Wilcoxon rank-sum and Pearson's chi-square test were used for continuous and categorical variables, respectively, to determine possible significant differences between cases and controls. To examine the relation of DR and CSII (improvement, worsening and need for ocular intervention) semi-adjusted (age and sex) and fully adjusted (age, sex and significant differences between cases and controls [marital status]) Cox regression models estimating hazard ratios (HR) were used. To utilize data from both eyes, clustered standard errors were applied. All data analyzes were completed using Stata 17.0 (StataCorp LLC, College Station, Texas, USA).

## 4. Results

Of all 22,530 individuals with type 1 diabetes in DiaBase we identified 5,137 who had any CSII treatment from 2013 to 2022 (prevalence 22.8 %). Of these, 674 individuals were included in our study population as cases, as they met the inclusion criteria (prevalence 3.0 %), had a screening close to CSII initiation and did not have any registration of CSII prior to first screening date in DiaBase. We matched these with 2006 comparable controls. The cohort was primarily female (53.4 %), had a median age of 36 years (IQR 27–47) and 38.5 % had pre-existing DR at index date with 24.9 %, 8.5 %, 0.6 % and 4.5 % having mild, moderate, severe DR and PDR respectively (Table 1). Cases were more often married (45.9 vs. 38.3 %), but did not differ from controls in regards to comorbidities (CCI score), duration of diabetes or glycemic stability at index date.

**Table 1**
Characteristics of included individuals using CSII and MDI at index date.

| | | Type of insulin | | |
|---|---|---|---|---|
| | Total | CSII | MDI | P-value |
| | $N = 2680$ | $N = 674$ | $N = 2006$ | |
| Age, years | 36 (27–47) | 36 (27–47) | 36 (27–47) | 0.93 |
| Sex, % female | 1432 (53.43 %) | 361 (53.56 %) | 1071 (53.39 %) | 0.94 |
| Duration of diabetes, year | 11.41 (5.42–17.55) | 11.75 (5.02–17.52) | 11.28 (5.48–17.56) | 0.70 |
| Marital status | | | | 0.002 |
| Never married | 1348 (50.30 %) | 311 (46.14 %) | 1037 (51.69 %) | |
| Married or living together | 1077 (40.19 %) | 309 (45.85 %) | 768 (38.29 %) | |
| Divorced or widow | 255 (9.51 %) | 54 (8.01 %) | 201 (10.02 %) | |
| CCI score | | | | 0.43 |
| 0 (low) | 2087 (77.87 %) | 517 (76.71 %) | 1570 (78.27 %) | |
| 1 (moderate low) | 484 (18.06 %) | 134 (19.88 %) | 350 (17.45 %) | |
| 2 (moderate high) | 82 (3.06 %) | 17 (2.52 %) | 65 (3.24 %) | |
| ≥3 (high) | 27 (1.01 %) | 6 (0.89 %) | 21 (1.05 %) | |
| Level of DR | | | | 0.85 |
| No DR | 1648 (61.49 %) | 412 (61.13 %) | 1236 (61.62 %) | |
| Mild NPDR | 667 (24.89 %) | 167 (24.78 %) | 500 (24.93 %) | |
| Moderate NPDR | 229 (8.54 %) | 58 (8.61 %) | 171 (8.52 %) | |
| Severe NPDR | 16 (0.60 %) | 6 (0.89 %) | 10 (0.50 %) | |
| PDR | 120 (4.48 %) | 31 (4.60 %) | 89 (4.44 %) | |
| HbA1c | 62 (53.0–73.0) | 63.0 (55.0;72.0) | 61.0 (52.0;73.0) | 0.23 |

Results given as counts (%), medians (IQR) and for HbA1c in mmol/mol.
CCI = Charlson Comorbidity Index, DR = diabetic retinopathy, NPDR = non proliferative DR, PDR = proliferative DR, CSII = continuous subcutaneous insulin infusion, MDI = multiple daily injections, IQR = interquartile range, ICDR = International Clinical DR severity scale, HbA1c = glycated hemoglobin.

During follow-up DR worsening was observed in 29.7 vs. 27.2 % of cases and controls respectively. DR improvement was observed in 5.7 % in both cases and controls. The need for ocular intervention of any kind was observed in 4.8 vs. 3.6 % of cases and controls respectively (Table 2). Average time at risk per person was 4.8 years and 5.1 years for DR worsening and ocular intervention respectively in both cases and controls (Table 2). In a fully adjusted Cox regression model, there was no significant difference in the risk of DR worsening between cases and controls short- (HR 0.82 [95%CI 0.50; 1.33], $p = 0.41$) or long-term (HR 1.05 [95%CI 0.91;1.22], $p = 0.49$) (Table 2). This risk was unaffected when the analyzes were stratified by the presence or absence of DR at index date. The need for ocular intervention during follow-up did not differ amongst cases or controls when pooled (HR 1.28 [95%CI 0.87;1.90], $p = 0.22$), but an isolated increased risk of focal photocoagulation was observed in cases (HR 2.40 [95%CI 1.11,5.19], $p = 0.03$).

Biochemical measurements, including lipids and kidney function were within reference limits and were not affected by the change in mode of insulin infusion, except for HbA1c and total cholesterol (Table 3). HbA1c was elevated beyond normal reference levels in both cases and controls both at index date and at follow up (7.9 % [63.0] vs. 7.7 % [61.0] and 7.5 % [59.0] vs. 7.7 % [61.0]), but a clear decline in HbA1c in cases was observed (Fig. 1), compared to HbA1c in controls which remained higher and more unstable over time (Fig. 1, Table 3). Total cholesterol was slightly elevated in both groups and remained so for the duration of follow-up (4.5 vs. 4.3 mmol/L and 4.4 vs. 4.4 mmol/L), even though a slight decline was observed in cases.

## 5. Discussion

The present study aimed to investigate short- and long-term development of DR in individuals with type 1 diabetes treated with CSII. Our findings did not reveal a significant difference in the risk of DR worsening between the individuals utilizing CSII treatment compared to users of MDI. The overall combined risk of ocular intervention was not higher in the CSII group compared to the MDI group, however, an isolated increased risk of focal photocoagulation was observed in the CSII group.

These results align with previous research that generally found CSII treatment to be safe in regards to DR.[6] Even though we observed a decline in HbA1c of 5.0 mmol/mol (0.4 % points) we did not see any increase in neither short- nor long-term DR. The risk of transient worsening is not as well described in individuals switching from MDI to CSII, maybe due to the increased glycemic stability, fewer hypoglycemic events and consistent insulin delivery that better mimic the natural insulin secretion.[21] Recent findings, like the ones presented in this study, are comparing CSII to MDI, whereas older studies comparing CSII to more conservative insulin injection regimens did find an increased risk of transient worsening.[22] The increased risk of focal photocoagulation found in our study could be considered contradictory to these results, as it would be suspected that this type of treatment is used in instances where the individual has developed diabetic macular edema (DME). Previous studies have shown a tendency of retinal thickening both following CSII initiation,[7] but also following bariatric surgery[23] – both instances where HbA1c can decrease rapidly and significantly. Even though a transient subclinical retinal thickening might be clinically negligible, some studies have shown an increased retinal thickening to be a predictive factor of macular edema.[24] DME codes were not available with satisfactory completeness in DiaBase and thus were not examined in detail, but the observation that the CSII group potentially has a higher risk of DME than MDI-treated controls warrants further investigation.

**Table 2**
Cox regression showing the risk of diabetic retinopathy worsening, diabetic retinopathy improvement and ocular intervention in individuals (at eye level) using continuous subcutaneous insulin injections (CSII) compared to individuals using multiple daily injections (MDI).

| | CSII eligible | Average risk-time for cases (years) | MDI eligible | Average risk-time for controls (years) | Events CSII | Events MDI | Hazard ratio (95 % CI) | Fully adjusted *P*-value[f] |
|---|---|---|---|---|---|---|---|---|
| Incident DR | 1284 | 4.9 | 3837 | 4.8 | 324 | 911 | 1.02 (0.87; 1.19) | 0.846 |
| Progression of DR | 1276 | 5.1 | 3811 | 5 | 167 | 458 | 1.04 (0.83; 1.30) | 0.730 |
| Progression to PDR | 1286 | 5.2 | 3836 | 5 | 44 | 87 | 1.28 (0.81; 2.02) | 0.285 |
| **DR improvement**[a] | **1286** | **4.2** | **3829** | **4.1** | **73** | **220** | **0.96 (0.70; 1.33)** | **0.825** |
| **DR worsening**[b] **short-term**[c] | **437** | **4.4** | **1131** | **4.4** | **32** | **100** | **0.83 (0.51; 1.35)** | **0.413** |
| **DR worsening long-term**[d] | **1284** | **4.8** | **3836** | **4.8** | **381** | **1043** | **1.05 (0.91; 1.22)** | **0.487** |
| Vitrectomy[e] | 1347 | 5.2 | 3998 | 5.1 | – | – | – | – |
| Panretinal photocoagulation | 1286 | 5.2 | 3869 | 5.1 | 49 | 106 | 1.37 (0.88; 2.13) | 0.170 |
| Focal photocoagulation | 1324 | 5.2 | 3945 | 5.1 | 17 | 20 | 2.40 (1.11; 5.19) | 0.026 |
| Anti VEGF | 1348 | 5.2 | 4009 | 5.1 | 26 | 59 | 1.24 (0.68; 2.27) | 0.482 |
| **Interventions pooled** | **1277** | **5.1** | **3830** | **5.1** | **61** | **139** | **1.28 (0.87; 1.90)** | **0.215** |

Results given as counts and hazard ratios (CI 95 %).
CI = confidence interval, DR = diabetic retinopathy, PDR = proliferative DR, VEGF = Vascular Endothelial Growth Factor.
[a] 2+ step regression of DR.
[b] Incident DR or 2+ step progression of DR.
[c] Outcome registered at six months following CSII initiation.
[d] Outcome registered at last recorded screening in DiaBase.
[e] Not analyzed due to too few events.
[f] Adjusted for sex, age and marital status.

Of the entire population in DiaBase with type 1 diabetes, we identified 22.8 % utilizing CSII. First and foremost it must be noted that many utilizing CSII are children, and thus not represented in DiaBase and our study. The prevalence might however also represent a potential restrictive approach to CSII treatment in Denmark, and might relate to the Danish national guidelines[25] for initiating CSII treatment which includes HbA1c >7.0 % (53.0) as well as one or more of the following 1) repeated episodes of hypoglycemia 2) failure to recognize the symptoms of hypoglycemia 3) nightly problems with regulation of the stability of blood glucose levels. CSII treatment must be initiated and monitored by an endocrinology department in a Danish hospital and patients must have a certain degree of insight into their own diabetes management and care to be able to manage the treatment on a daily basis. Furthermore, the prevalence could be attributed to the Danish Healthcare system's economic prioritization. However, a British systematic review[26] examining the cost-effectiveness of CSII treatment compared to MDI treatment across several countries, including Denmark,[27] concluded that CSII treatment can be considered cost-effective and with improvements to quality of life, especially when the group utilizing it is similar to the group which is currently recommended CSII in Denmark. When assessing the implementation of CSII use, quality of life in patients with type 1 diabetes is a factor that should not be neglected, as it adds to the benefits of CSII use beyond improves glycemic control. Several studies document how the use of CSII treatment improves treatment satisfaction and health perception, as well as provides an increased convenience of daily living.[28,29]

Recent studies on CGM and Time in Range (TIR, time spend within target range of blood glucose) provide additional context. Studies have shown that better TIR is associated with lower risk of DR progression, emphasizing the importance of glycemic stability in managing DR.[10,11] Combining CSII with CGM could further enhance outcomes by providing real-time glucose data and more precise insulin adjustments, thus potentially reducing DR risk.[12]

A major strength of our study lies in the use of a large register- and population-based cohort, allowing us to access a substantial number of individuals with type 1 diabetes and compare outcomes between CSII-treated individuals and controls. The matching done based on age, sex, and DR level enhances the comparability of the groups and reduces potential confounding factors. Additionally, the long-term follow-up period provides valuable insights into the incidence and progression of DR in this population. However, limitations should also be acknowledged. First, the study relied on data from the Danish screening program for DR, which is an optional, but recommended program, meaning that not all individuals with diabetes choose to attend. Potential self-selection bias could affect the generalizability of our findings, as individuals who participated in the screening program may differ from those who did not. Second, potential misclassification might also be considered, no matter how thorough and rigorous the process of designing the study and selecting the criteria for group-selection. In this study, this could be relevant to both the diabetes type, the definition of cases and controls, as well as the definition of ocular surgical outcomes. Finally we must acknowledge the fact that due to the register-based nature of the study, information regarding the study participants are limited to the data available in the registers; thus data on i.e. blood pressure and body mass index were not accessible.

In conclusion, our study found no significant difference in the risk of DR worsening between individuals with type 1 diabetes treated with CSII and the control group utilizing MDI. Further research is needed to better understand the implications of CSII treatment on the progression of DR and especially regarding the potential increased need of photocoagulation, considering the impact of various factors beyond glycemic control. These efforts can hopefully guide future research, clinical decision-making, and the development of personalized treatment approaches for individuals with type 1 diabetes and DR.

## Author contributions and guarantor statement

J.G., N.A., J.A., T.B., S.H., C.S.L., and K.C.S. contributed research

**Table 3**
Biochemical measurements and pharmaceutical treatments for individuals with continuous subcutaneous insulin injections (CSII) and individuals with multiple daily injections (MDI) at equal time-points.

| | Index date[a] | | | | | Follow-up[b] | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Individuals with measurements (CSII) | Median (IQR) | Individuals with measurements (MDI) | Median (IQR) | P-value | Individuals with measurements (CSII) | Median (IQR) | Individuals with measurements (MDI) | Median (IQR) | P-value |
| Biochemical | | | | | | | | | | |
| HbA1c | 593 (0.88) | 7.9 (7.2;8.7) (63.0 [55.0;72.0]) | 1673(2.48) | 7.7 (6.9;8.8) (61.0 [52.0;73.0]) | 0.23 | 557(0.83) | 7.5 (6.8;8.3) (59.0 [51.0;67.0]) | 1653(2.45) | 7.7 (7.0;8.6) (61.0 [53.0;71.0]) | <0.001 |
| Lipids | | | | | | | | | | |
| Triacylglycerol | 497 (0.74) | 0.92 (0.66;1.36) | 1397(2.07) | 1.00 (0.70;1.50) | <0.001 | 504(0.75) | 0.90 (0.68;1.28) | 1502(2.23) | 1.00 (0.73;1.43) | <0.001 |
| HDL | 499( 0.74) | 1.50 (1.20;1.80) | 1395(2.07) | 1.50 (1.20;1.80) | 0.85 | 504(0.75) | 1.50 (1.30;1.80) | 1497(2.22) | 1.50 (1.20;1.80) | 0.07 |
| LDL | 497 (0.74) | 2.40 (2.00;3.00) | 1391(2.06) | 2.40 (1.90;2.90) | 0.03 | 503(0.75) | 2.30 (1.90;2.80) | 1488(2.21) | 2.30 (1.80;2.90) | 0.78 |
| Total cholesterol | 499 (0.74) | 4.50 (3.90;5.10) | 1400(2.08) | 4.40 (3.90;5.00) | 0.24 | 504(0.75) | 4.30 (3.80;4.90) | 1499(2.22) | 4.40 (3.80;5.00) | 0.34 |
| Nephrology | | | | | | | | | | |
| eGFR | 527 (0.78) | 90.00 (89.00;90.00) | 1511(2.24) | 90.00 (90.00;90.00) | 0.75 | 569(0.84) | 90.00 (90.00;90.00) | 1708(2.53) | 90.00 (90.00;90.00) | 0.01 |
| Plasma creatinine | 552 (0.82) | 67.00 (59.00;77.00) | 1576(2.34) | 66.00 (57.00;77.00) | 0.06 | 582(0.86) | 69.50 (61.00;79.00) | 1737(2.58) | 67.00 (58.00;77.00) | <0.001 |
| uACR | 438 (0.65) | 6.00 (4.00;13.00) | 1121(1.66) | 7.00 (4.00;16.00) | 0.01 | 502(0.74) | 6.00 (3.54;11.00) | 1366(2.03) | 7.00 (4.00;16.00) | <0.001 |

Results are given in counts (%), medians with interquartile range (IQR). HbA1c given in % (mmol/mol), triacylglycerol, HDL, LDL and total cholesterol is given ad mmol/L. eGFR is given as mL/min/1.73m$^2$. Plasma creatinine is given as μmol/L. uACR is given as mg/g.

HbA1c = glycated hemoglobin, HDL = high density lipoprotein, LDL = low density lipoprotein, eGFR = glomerular filtration rate, uACR = urine albumin/creatinine ratio, IQR = interquartile range.

[a] Closest registration prior to initiation of CSII (within one year).

[b] Follow-up = measurement closest to 36 months post CSII initiation.

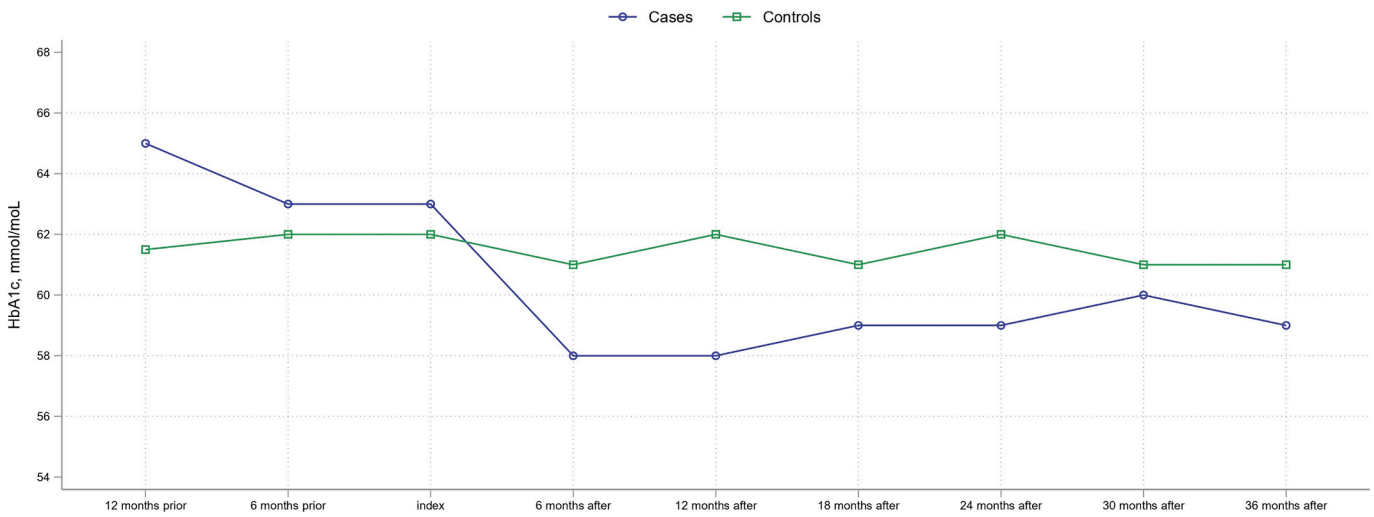


**Fig. 1.** HbA1c levels in individuals with continuous subcutaneous insulin injections (CSII, blue) and with multiple daily injections (MDI, green) at fixed time points. Index date = time of first registration of CSII treatment, HbA1c = glycated hemoglobin.

data. J.G., A.S.T., R.K., K.H. and L.S. designed and conceptualized the study. A.S.T. wrote the first draft of the manuscript. All co-authors reviewed and accepted the final draft of the manuscript. A.S.T. 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.

## Compliance with ethical standards

This study was performed in accordance with the principles of The Declaration of Helsinki. No ethical approvals or informed consent agreements were needed, due to the observational, register-based design of the study.

## CRediT authorship contribution statement

**Anne S. Thykjær:** Writing – review & editing, Writing – original draft, Visualization, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization. **Louise Rosengaard:** Writing – review & editing, Formal analysis. **Nis Andersen:** Writing – review & editing, Data curation, Conceptualization. **Jens Andresen:** Writing – review & editing, Data curation, Conceptualization. **Javad Hajari:** Writing – review & editing. **Steffen Heegaard:** Writing – review & editing, Data curation, Conceptualization. **Kurt Højlund:** Writing – review & editing, Data curation, Conceptualization. **Ryo Kawasaki:** Writing – review & editing, Data curation, Conceptualization. **Caroline S. Laugesen:** Writing – review & editing, Data curation, Conceptualization. **Sören Möller:** Writing – review & editing, Data curation, Conceptualization. **Frederik N. Pedersen:** Writing – review & editing. **Katja Schielke:** Writing – review & editing, Data curation, Conceptualization. **Lonny M. Stokholm:** Writing – review & editing, Supervision, Methodology, Formal analysis, Data curation, Conceptualization. **Jakob Grauslund:** Writing – review & editing, Supervision, Funding acquisition, Data curation, Conceptualization.

## Declaration of competing interest

None.

## Data availability

The data that support the findings of this study are available from the Danish Health Data Authority, but restrictions apply to the availability of these data, which were used under license from OPEN and the Danish Health Data Authority for the current study and therefore are not publicly available.

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## Appendix 1. Classification of diabetes type, developed by the Ocular And Systemic complications In diabetic retinopathy (OASIS) study group, to be used for Danish register-based studies

In a generic, non-selected population (National Patient Registry)

| | |
|---|---|
| Type 1 diabetes | Latest given diagnostic code must be DE10<br>AND<br>First prescription of A10A within a year of first DE10 diagnosis*<br>AND<br>Last prescription of A10A within a year of exit<br>AND number of prescriptions ≥ number of years from first prescription to exit |

(*continued on next page*)

(*continued*)

| | |
|---|---|
| Type 2 diabetes | Diagnostic code DE11<br>AND<br>≥ two A10B prescriptions**<br><br>OR<br><br>≥ two DE11 diagnostic codes<br><br>OR<br><br>≥ two prescriptions of A10A if age 40+ at prescription<br><br>OR<br><br>≥ two prescriptions of A10B if age 30+ at prescription<br><br>*Exclusions:*<br><br>*Already grouped as type 1 diabetes*<br><br>*OR/AND*<br><br>*Female AND diagnostic code for PCOS (E282) AND no diagnostic code for diabetes type II (DE11)* |

In a population consisting exclusively of patients presumed to have diabetes (DiaBase)

| | |
|---|---|
| Type 1 diabetes | Latest given diagnostic code in The National Patient Register = DE10*<br>AND<br>First prescription of A10A within a year of first DE10 diagnosis<br>AND<br>Last prescription of A10A within a year of exit<br>AND number of prescriptions ≥ number of years from first prescription to exit |
| Type 2 diabetes | The remaining population |

DiaBase = Danish Registry of Diabetic Retinopathy.
*Since data from The Danish National Prescription Registry is available from 1995 and onward, patients with a diagnosis given before this year and prescriptions starting in 1995, could be excluded unnecessarily. In the case of diagnosis given before 1995, the first prescription must therefore be in 1995; **One prescription is allowed for patients who received their diagnosis during 2022.

## References


1. JWY Y, Rogers SL, Kawasaki R, Lamoureux EL, Kowalski JW, Bek T, et al. Global Prevalence and Major Risk Factors of Diabetic Retinopathy. *Diabetes Care*. 10. februar 2012;35:556–564.
2. Tarasewicz D, Conell C, Gilliam LK, Melles RB. Quantification of risk factors for diabetic retinopathy progression. *Acta Diabetol marts*. 2023;60.
3. Wang W, Lo AC. Diabetic retinopathy: pathophysiology and treatments. *Int J Mol Sci juni*. 2018;19:1816.
4. Diabetes Control and Complications Trial Research Group. Effect of intensive diabetes treatment on the development and progression of long-term complications in adoles- cents with insulin-dependent diabetes mellitus: diabetes control and complications trial. *J Pediatr august*. 1994;125:177–188.
5. The Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) Study Research Group. Intensive Diabetes Treatment and Cardiovascular Outcomes in Type 1 Diabetes: The DCCT/EDIC Study 30-Year Follow-up. *Diabetes Care*. 9. februar 2016;39:686–693.
6. Virk SA, Donaghue KC, Wong TY, Craig ME. Interventions for diabetic retinopathy in type 1 diabetes: systematic review and Meta-analysis. *Am J Ophthalmol*. November 2015;160.
7. Klefter NO, Hommel E, Munch IC, Nørgaard K, Madsbad S, Larsen M. Retinal characte- ristics during 1 year of insulin pump therapy in type 1 diabetes: a prospective, controlled, observational study. *Acta Ophthalmol*. September 2016;94.
8. Dovc K, Battelino T. Evolution of diabetes technology. *Endocrinol Metab Clin North Am marts*. 2020;49.
9. Bain SC, Klufas MA, Ho A, Matthews DR. Worsening of diabetic retinopathy with rapid improvement in systemic glucose control: a review. *Diabetes Obes Metab marts*. 2019;21:454–466.
10. Shah VN, Kanapka LG, Akturk HK, Polsky S, Forlenza GP, Kollman C, et al. Time in range is associated with incident diabetic retinopathy in adults with type 1 diabetes: a longitudinal study. *Diabetes Technol Ther*. April 2024;26:246–251.
11. Liu TYA, Shpigel J, Khan F, Smith K, Prichett L, Channa R, et al. Use of Diabetes Technologies and Retinopathy in Adults With Type 1 Diabetes. *JAMA Netw Open*. 6. marts 2024;7, e240728.
12. Kovatchev B. Glycemic Variability: Risk Factors, Assessment, and Control. *J Diabetes Sci Technol*. 1. juli 2019;13:627–635.
13. Kampmann U, Madsen LR, Bjerg L, Witte DR, Hasselstrøm K, Østergård T, et al. Prevalence and geographical distribution of insulin pump therapy in the Central Denmark region and its association with metabolic parameters. *Diabetes Res Clin Pract*. Juli 2018:141.
14. Renard E. Insulin pump use in Europe. *Diabetes Technol Ther juni*. 2010;12:1.
15. Andersen N, Hjortdal JØ, Schielke KC, Bek T, Grauslund J, Laugesen CS, et al. The Danish registry of diabetic retinopathy. *Clin Epidemiol*. Oktober 2016;8:613–619.
16. Schmidt M, Schmidt SAJ, Sandegaard JL, Ehrenstein V, Pedersen L, Sørensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. *Clin Epidemiol november*. 2015;7:449–490.
17. Kildemoes HW, Sørensen HT, Hallas J. The Danish National Prescription Registry. *Scand J Public Health juli*. 2011;39:38–41.
18. Arendt JFH, Hansen AT, Ladefoged SA, Sørensen HT, Pedersen L, Adelborg K. Existing data sources in clinical epidemiology: laboratory information system databases in Denmark. *Clin Epidemiol maj*. 2020;12:469–475.
19. Schmidt M, Pedersen L, Sørensen HT. The Danish civil registration system as a tool in epidemiology. *Eur J Epidemiol august*. 2014;29:541–549.
20. Grauslund J, Stokholm L, Kyvik KO, de la Cour MD, Kessel L, Rubin KH. Interactions between ocular and systemic disease using national register-based data in the Danish excellence Centre in Ophthalmic Epidemiology (DECODE-EYE): study perspective. *Acta Ophthalmol*. September 2020;98:573–578.
21. Holfort SK, Nørgaard K, Jackson GR, Hommel E, Madsbad S, Munch IC, et al. Retinal function in relation to improved glycaemic control in type 1 diabetes. *Diabetologia*. juli 2011;54:1853–1861.
22. Brinchmann-Hansen O, Dahl-Jørgensen K, Hanssen KF, Sandvik L. The response of diabetic retinopathy to 41 months of multiple insulin injections, insulin pumps, and conventional insulin therapy. *Arch Ophthalmol september*. 1988;106:1242–1246.
23. Brynskov T, Laugesen CS, Svenningsen AL, Floyd AK, Sørensen TL. Monito- ring of diabetic retinopathy in relation to bariatric surgery: a prospective observational study. *Obes Surg*. 2016;26:1279–1286.
24. Lobo C, Pires I, Alves D, Pappuru R, Ribeiro L, Cunha-Vaz J. Subclinical macular edema as a predictor of progression to central-involved macular edema in type 2 diabetes. *Ophthalmic Res*. 2018;60:18–22.
25. National Clinical Guidelines for the use of insulin pumps in Denmark. In: *The Danish National Board of Health*. 2012:1–2.

26. Roze S, Smith-Palmer J, Valentine W, Portu S, de K Nørgaard, Pickup JC. Cost-effectiveness of continuous subcutaneous insulin infusion versus multiple daily injections of insulin in type 1 diabetes: a systematic review. *Diabet Med*. 2015;32: 1415–1424.
27. Nørgaard K, Sohlberg A, Goodall G. Cost-effectiveness of continuous subcu- taneous insulin infusion therapy for type 1 diabetes. *Ugeskr Laeger*. 2010;172:2020–2025.
28. Hussain T, Akle M, Nagelkerke N, Deeb A. Comparative study on treatment satisfaction and health perception in children and adolescents with type 1 diabetes mellitus on multiple daily injection of insulin, insulin pump and sensor-augmented pump therapy. *SAGE Open Med*. 2017;5, 2050312117694938.
29. Maiorino M, Bellastella G, Petrizzo M, Improta M, Brancario C, Castaldo F. m.fl. Treatment satisfaction and glycemic control in young type 1 diabetic patients in transition from pediatric health care: CSII versus MDI. *Endocrine*. 2013:46.