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Original Article

# Incidence of acute Charcot foot in patients with diabetes

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## ABSTRACT

**INTRODUCTION.** Acute Charcot foot is a rare but serious complication of diabetes mellitus. With improved diabetes treatment, the annual incidence of acute Charcot foot may have decreased. This study aimed to investigate the annual incidence and incidence rate of acute Charcot foot in patients with an ICD diagnosis code of diabetes in Denmark from 2000 to 2021. Furthermore, the analyses included differences between the five Danish regions. Finally, the impact of the COVID-19 pandemic and the nurses' strike in the summer of 2021 in Denmark was also examined.

**METHODS.** This was a register-based study conducted in Denmark from 2000 to 2021. Nation-wide and regional, annual incidence and incidence rates of acute Charcot foot were calculated. Kendall's tau was used to test changes in incidence rates.

**RESULTS.** A significant increase was found in the annual incidence of acute Charcot foot with a correlation of 0.6 ($p < 0.0005$) together with a decline in the annual incidence rate of acute Charcot foot (correlation of −0.6 with $p = 0.0005$). No differences were observed between theDanish regions. No change in acute Charcot foot incidence rate among diabetes patients was found during 2018-2021 (correlation of 0.3; $p = 0.5$).

**CONCLUSION.** The annual incidence increased, whereas the annual incidence rate of acute Charcot foot in patients with an ICD diagnosis code of diabetes in Denmark declined during 2000-2021, with no significant regional differences or change during the COVID-19 and nurses' strike.

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**TRIAL REGISTRATION.** Not relevant.

Charcot foot, also known as neuropathic osteoarthropathy, is a serious and disabling complication of diabetic neuropathy [1]. Acute Charcot foot presents as a warm, red and swollen foot, with inflammation of bones and joints, which can cause deformities, foot ulcers, amputations and even death without timely diagnosis and treatment [2].

The treatment consists of long-term off-loading of the Charcot foot with either a non-removable total contact cast (TCC), i.e. "the gold standard", or with a removable walker cast, such as Aircast Diabetic Walker [2]. Previous studies have indicated increased bone metabolism, osteoclast activity, bone resorption and inflammation in those with acute Charcot foot, with increased cytokine biomarkers for inflammation and bone resorption [2, 3]. Clinical trials with drugs against osteoporosis, such as bisphosphonates, have shown no clinical effect on acute Charcot foot [4]. However, inhibiting bone resorption and inflammation by targeting the receptor activator of the nuclear factor kappa-B ligand/osteoprotegerin (RANKL/OPG) system may be an effective treatment. Denosumab

is a monoclonal antibody against RANK-L, which is approved for the treatment of osteoporosis [2], and a Danish randomised, controlled trial of the effect of denosumab treatment on acute Charcot foot in patients with diabetes [4] is currently recruiting.

We have previously reported the incidence rate of acute Charcot foot in patients with diabetes in Denmark [5]. However, the incidence rate of neuropathy in patients with diabetes in Denmark has declined during the past decade [6]. Thus, the incidence rate of neuropathy-related acute Charcot foot may also have decreased. Therefore, the present study aimed to investigate whether the annual incidence and incidence rates of acute Charcot foot in patients with diabetes have declined from 2000 to 2021. With respect to annual incidence and incidence rates of acute Charcot foot in patients with diabetes, differences between the Danish regions were also examined. Additionally, the study explored the impact on the incidence rate of special circumstances, such as the COVID-19 pandemic and the nurse strike in Denmark in the summer of 2021.

## Methods

### Design

This was a nationwide, register-based cohort study that calculated the annual incidences and incidence rates of acute Charcot foot in diabetes patients.

### Data sources

The Danish National Patient Register (NPR) was used as the data source for the study population. Data concerning all hospitalisations, outpatient visits and emergency department contacts have been documented in the NPR since 1995 [7]. Furthermore, data from the Danish Civil Registration System was used to obtain information regarding age, sex, immigration and emigration [8]. All Danish nationals and residents born or residing in Denmark are assigned a unique identification number, commonly referred to as “CPR”. Healthcare and public authorities use this identification number in all interactions, enabling the connection of civil and health register data. Death dates were retrieved from the Death Register (DR) maintained by Statistics Denmark [9].

### Study cohort

The study population comprised diabetes patients and patients with acute Charcot foot. To calculate person-years to determine incidence rates of acute Charcot foot among diabetes patients, all the diabetes patients who had contacted the hospitals in the study period were found. These patients had one or more of the International Classification of Diseases, 10$^{th}$ version (ICD-10) diabetes diagnosis code elements: DE10.X (type 1 diabetes mellitus), DE11.X (type 2 diabetes mellitus), DE13.X (other specified diabetes mellitus) and DE14.X (other unspecified diabetes mellitus). Moreover, the population included patients with one or more diabetes-related ICD-10 diagnosis codes, including DH360 (diabetic retinopathy), DH159 (disorder of sclera), DG632 (diabetic polyneuropathy), DH280 (diabetic cataract) in Denmark during the period from 1 January 2000 to 31 December 2021 [10]. Data for each patient from the NPR, CPR and DR were linked using anonymised versions of the Danish ID numbers.

Patients with diabetes or diabetes-related diagnoses with a closed hospital contact concerning diabetes before 1 January 2000 were excluded, as the data were available only for the 2000-2021 period. Patients who received a diabetes-related diagnosis after their date of death or who had emigrated during the study period were also excluded.

To determine the incidence of acute Charcot foot, patients were identified as having a new ICD-10 code DM142

(diabetic arthropathy) and/or DM146 (neuropathic arthropathy) from 1 January 2000 to 31 December 2021. Patients who already had a Charcot foot diagnosis before the study period started but were in treatment or active contact during the study period were excluded, as were patients who had received a diagnosis after their date of death. If the patients had emigrated during the study period, their emigration date was the last follow-up day. As previously reported [3], it was not possible to achieve valid results for the different types of diabetes.

To determine incidence rates, person-years were calculated using the first date of diabetes-related diagnosis and the date of death, emigration or diagnosis of Charcot foot as the exit date. Incidence and incidence rates were calculated annually for the whole country from 2000 to 2021. Incidence rates of acute Charcot foot during the study period were then measured for each of the five regions of Denmark and for the five sub-periods region-wise: 2000-2004, 2005-2009, 2010-2013, 2014-2017 and 2018-2021. Finally, to monitor the impact of the COVID-19 pandemic and the nurses' strike in Denmark in the summer of 2021, changes in the incidence rate were calculated for 2018-2021.

### Outcome and covariates

Using the National Patient Registry, ICD-10 codes, exposure, outcome and covariates (sex, age and Danish region) were determined. The first outcome, "diabetes", was defined as any patient having one of the following diabetes-related ICD-10 codes: DE10, DE11, DE13, DE14, DH360, DH159, DG632, DH280. The second outcome, "Charcot foot", was identified as patients with either ICD-10 code DM142 or DM146. Although the diagnosis of Charcot foot cannot always be confirmed and it may sometimes be incorrectly coded, for example, as DG60.0 (Charcot-Marie-Tooth), these errors were presumed to have remained stable throughout the study period.

### Statistical analysis

Frequencies and percentages were used to sum up categorical values. The median and the 25th and 75th percentile were used to summarise continuous variables. Confidence intervals were calculated using the Poisson-test function in R for the incidence rate to test for any overlap between incidence rates [11]. The $\chi^2$ test was used to determine any significant difference between diabetes patients with and without acute Charcot foot (categorical data). To test for significance between different groups (continuous and categorical data), the Kendall's tau tests were performed. Data analysis and management were performed using SAS 9.4 software (SAS Institute, Cary, NC). Statistical significance was defined as p values < 0.05. Statistical software "R" version 4.2.2. and Microsoft Excel were used for data representation [11].

### Ethics

Study approval was received from the Capital Region, Denmark (P-2019-23). Data containing personal information was well protected, as it had been anonymised and was accessed via an encrypted server provided by Statistics Denmark. Register-based studies do not require approval from an ethics committee in Denmark.

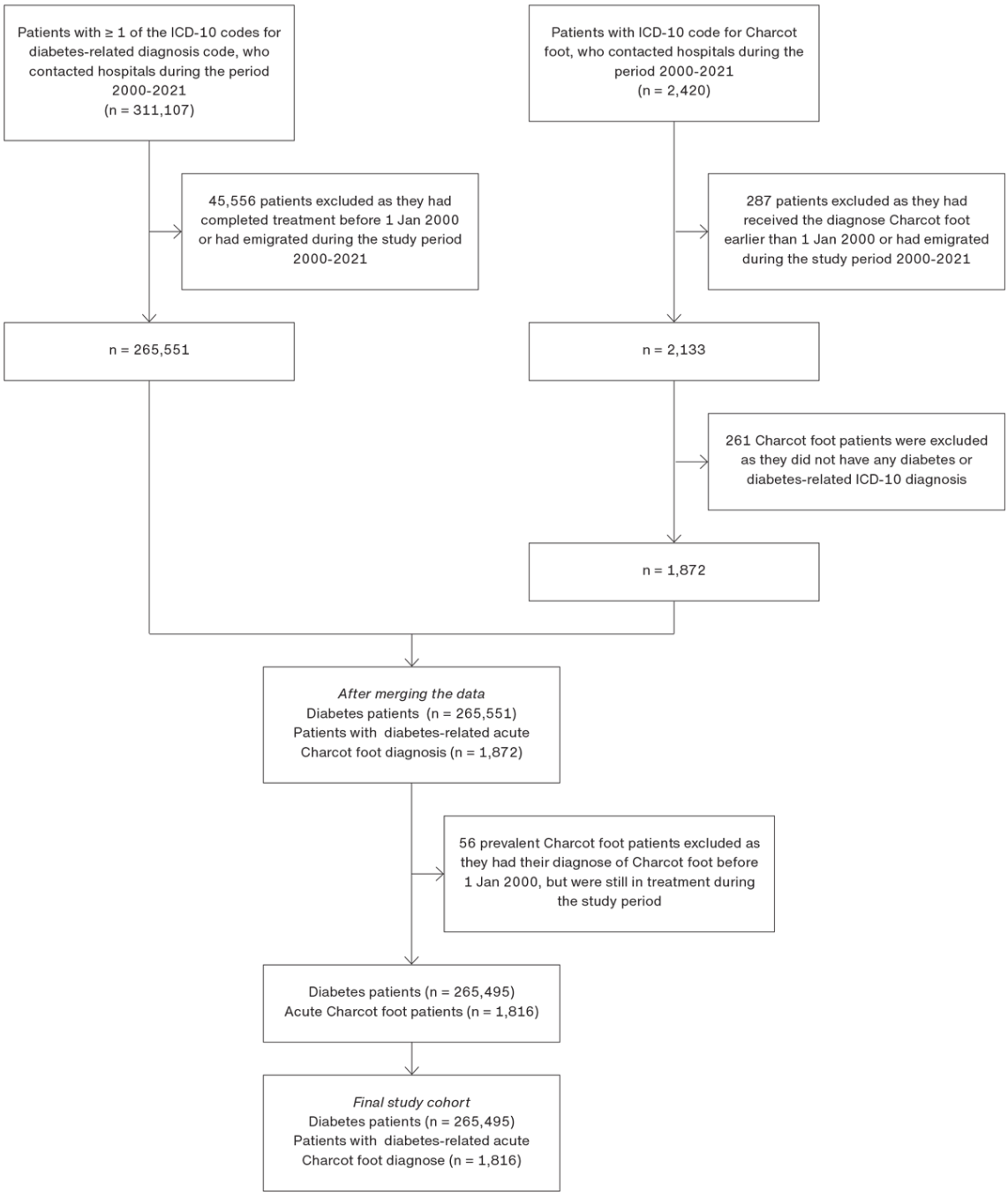
*Trial registration:* not relevant.

## Results

**Figure 1** shows the patients' inclusions and exclusions. The population studied consisted of 1,816 patients with diabetes and acute Charcot foot and 265,495 patients with diabetes without acute Charcot foot.

**FIGURE 1** Flow chart showing inclusion and exclusion of patients in the study.




### Population characteristics

More men (56%) than women (44%) had diabetes, and more men (65%) than women (35%) with diabetes had acute Charcot foot ($p < 0.001$). The prevalence of acute Charcot foot among diabetes patients in Denmark was 0.68% from 2000 to 2021. The median patient age when first diagnosed with acute Charcot foot was 60 years (25th and 75th percentile: 52-68 years). The patients with acute Charcot foot were younger when they were diagnosed with diabetes (median 53 years (42-61 years)) than those without acute Charcot foot (median 63 years (51-73 years)). The median time from diagnosis of diabetes to diagnosis of Charcot foot was eight years (3-11 years).

### Annual incidence in Denmark

The annual incidence of acute Charcot foot in patients with diabetes in Denmark, shown in **Table 1**, increased from 2000 to 2021 (Kendall's tau correlation: 0.6; $p < 0.0005$). It primarily increased from 2000-2009 with a Kendall's tau of 0.9 ($p < 0.0005$), whereas there was no change in the annual incidence from 2010-2021 (Kendall's tau: −0.2; $p = 0.3$).

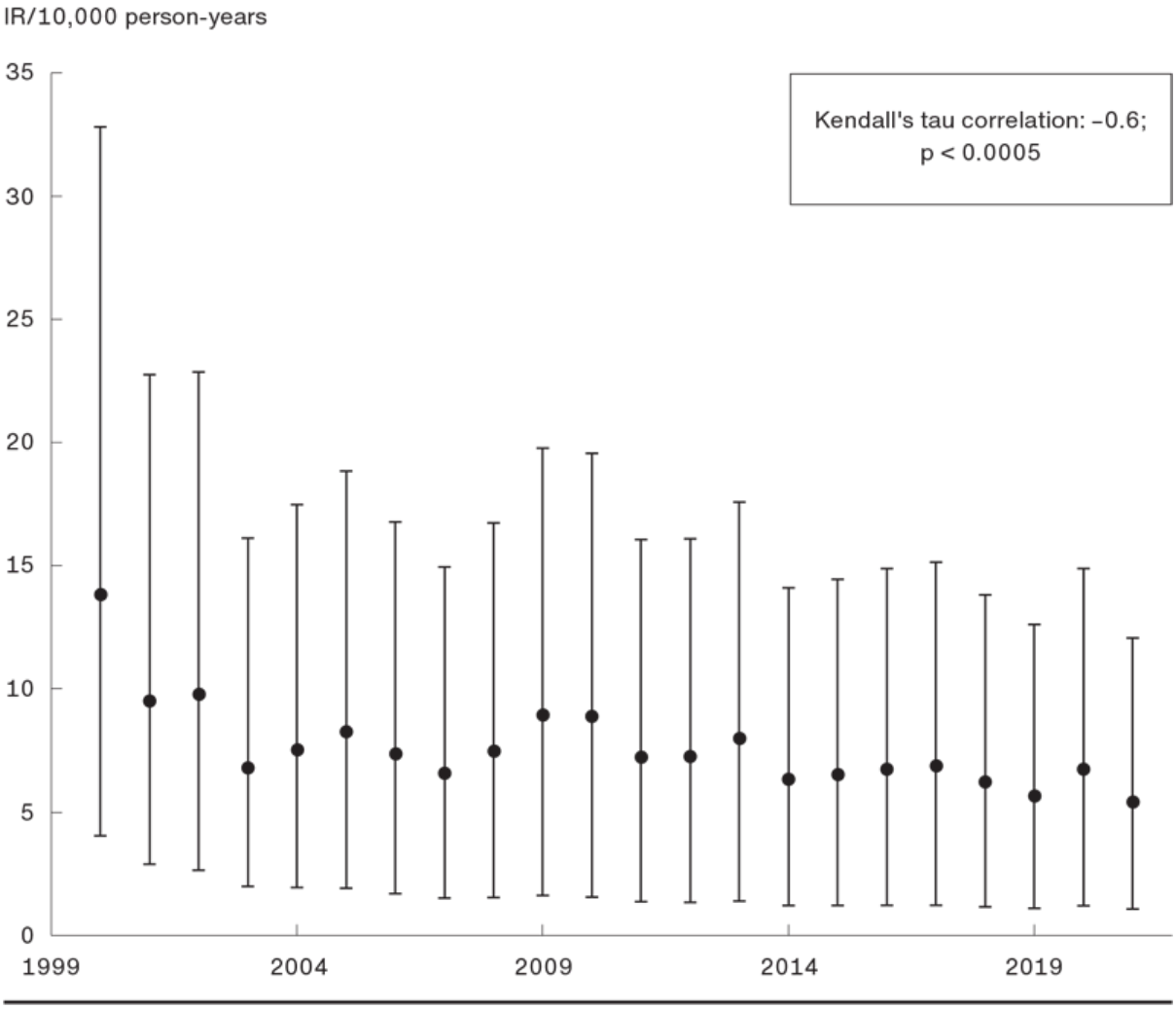
**TABLE 1** Annual incidence and incidence rate of acute Charcot foot in patients with diabetes in Denmark during the period from 2000 to 2021.

| Year | Incidence of new cases, n | Person-years, n | Incidence rate | Incidence rate per 10,000 person-years |
|---|---|---|---|---|
| 2000 | 38 | 27,479.00 | 0.001383 | 13.8 |
| 2001 | 35 | 36,771.29 | 0.000952 | 9.5 |
| 2002 | 45 | 46,018.79 | 0.000978 | 9.8 |
| 2003 | 38 | 55,921.79 | 0.000680 | 6.8 |
| 2004 | 50 | 66,304.04 | 0.000754 | 7.5 |
| 2005 | 63 | 76,219.81 | 0.000827 | 8.3 |
| 2006 | 64 | 86,850.70 | 0.000737 | 7.4 |
| 2007 | 64 | 97,474.98 | 0.000657 | 6.6 |
| 2008 | 81 | 108,537.54 | 0.000746 | 7.5 |
| 2009 | 107 | 119,510.70 | 0.000895 | 9.0 |
| 2010 | 114 | 128,297.40 | 0.000889 | 8.9 |
| 2011 | 97 | 134,041.64 | 0.000724 | 7.2 |
| 2012 | 102 | 140,319.45 | 0.000727 | 7.3 |
| 2013 | 116 | 145,075.30 | 0.000800 | 8.0 |
| 2014 | 95 | 149,674.73 | 0.000635 | 6.3 |
| 2015 | 100 | 153,373.17 | 0.000652 | 6.5 |
| 2016 | 106 | 157,329.80 | 0.000674 | 6.7 |
| 2017 | 110 | 160,164.53 | 0.000687 | 6.9 |
| 2018 | 101 | 161,891.91 | 0.000624 | 6.2 |
| 2019 | 92 | 162,354.68 | 0.000567 | 5.7 |
| 2020 | 110 | 162,919.83 | 0.000675 | 6.8 |
| 2021 | 88 | 162,718.16 | 0.000541 | 5.4 |
| 2000-2021 | 1,816 | 2,539,249.24 | 0.000715 | 7.2 |

**Annual incidence rate in Denmark**

Table 1 also presents the annual incidence rates of acute Charcot foot in patients with an ICD diagnosis of diabetes in Denmark from 2000 to 2021. An overall incidence rate of 7.2 per 10,000 person-years was found for acute Charcot foot in patients with diabetes patients in Denmark between 2000 and 2021. The annual incidence rate of acute Charcot foot per 10,000 patient-years in patients with diabetes is presented in **Figure 2**. A significant decrease was observed in the annual incidence rates from 2000 to 2021 (Kendall's tau: −0.6; $p = 0.0005$).

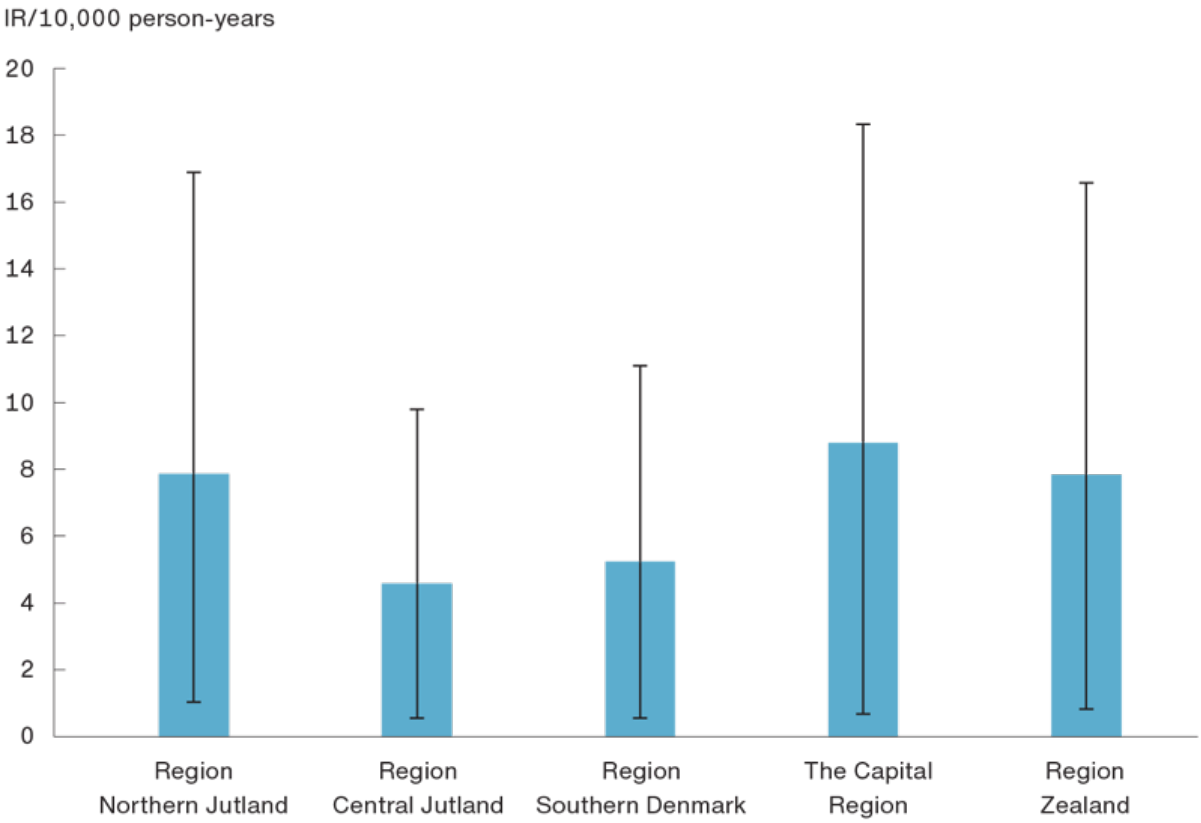
**FIGURE 2** Annual incidence rate (IR) of acute Charcot foot in patients with diabetes during the period from 2000 to 2021.




**Incidence rates in the five Danish regions**

As shown in **Figure 3**, the incidence rates of acute Charcot foot in patients with diabetes did not differ between the five Danish regions from 2000 to 2021 ($p = 0.55$).

**FIGURE 3** Incidence rate (IR) per 10,000 person-years of acute Charcot foot among diabetes patients in the five Danish regions during the period from 2000 to 2021.




Impact of the COVID-19 pandemic and the nurses' strike in the summer 2021 When comparing annual incidence rates of acute Charcot foot among diabetes patients in the years from 2018 to 2021, no significant differences were observed (Kendall's tau: −0.3; p = 0.5).

## Discussion

This study is the first and the most extensive ever to investigate nationwide changes over time in annual incidences and incidence rates of acute Charcot foot in patients with diabetes.

The main finding of the present study is an increase in annual incidence but a reduction in annual incidence rates of acute Charcot foot in patients with diabetes in Denmark in the 2000-2021 period. This means that the risk of getting an acute Charcot foot for an individual patient with diabetes has decreased. However, due to the ever-increasing number of patients with diabetes, with an expected 32% increase to 784 million worldwide in 2045 [12], the annual incidence of acute Charcot foot in society has increased. However, the increase in annual incidence seems primarily to have occurred from 2000 to 2009, whereas the annual incidence appears to have remained stable from 2010 to 2021. These findings confirm other studies showing that the incidence rates of complications to diabetes, such as neuropathy, myocardial infarction, stroke, lower-extremity amputation, end-stage renal disease and death, have decreased due to improved diabetes treatment [6, 13, 14].

In Denmark, regional differences exist in the incidence rates of lower extremity amputations, probably due to differences in the health care provided [15]. However, we found no significant differences in the incidence rates of acute Charcot foot between the five Danish regions, suggesting fewer differences in the healthcare provided

across the five regions regarding diabetes and the prevention of acute Charcot foot in patients with diabetes.

Of the 2,077 patients with ICD-10 codes for Charcot foot from 2000 to 2021, 261 did not have a diabetes diagnosis (but might have had diabetes). This implies that up to 13% of Charcot foot diagnoses are not diabetes-related but occur due to other illnesses, such as alcoholism, spinal stenosis, spinal tumour, neurodevelopmental defect, Charcot-Marie-Tooth, side effects of anti-HIV medication and other unknown diseases, as described previously [1].

There was no significant impact on the annual incidence rates of acute Charcot due to the COVID-19 lockdown or staff shortages caused by the nurses' strike. This may be explained by the fact that acute Charcot foot is an acute foot condition that requires urgent treatment by a hospital-based multidisciplinary team [16] without postponement and which was, therefore, treated accordingly. If the diabetes treatment during that period were less than optimal, it would likely have taken some time to develop an acute Charcot foot as a result.

### Limitations

Patients without hospital contact during the study period were excluded from the present study. Consequently, data were unavailable for patients with type 2 diabetes who had been managed by their general practitioner only. Furthermore, the prevalence of the total population of patients with type 2 diabetes, including those not seen at hospitals, has increased [17]. This may have led to an overestimation of the incidence rates of acute Charcot foot in the total population of diabetes patients. This selection bias will not affect the number of acute Charcot foot patients as the illness is severe, and the patients would need to contact the hospital as treatment by one's general practitioner would be insufficient. Furthermore, a relatively higher incidence rate for the year 2000 was observed, possibly due to prevalent Charcot foot cases from before 2000. Nonetheless, this does not appear to influence the incidence rates for the remaining years included in this study.

## Conclusion

The annual incidence increased, whereas the annual incidence rate of acute Charcot foot in patients with an ICD 10 diagnosis of diabetes in Denmark declined from 2000 to 2021.

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