Outcomes in patients with chronic leg wounds in Denmark: A nationwide register-based cohort study

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Abstract
This study aimed to investigate incidence and predictors of wound healing, relapse, major amputation, and/or death among patients with chronic leg wounds who were referred to specialist treatment at hospital for their condition. A nationwide register-based cohort study design was applied with 5 years of follow-up. All patients with diagnoses of chronic leg wounds in Denmark between 2007 and 2012 were included (\(n = 8394\)). Clinical, social, and demographic individual-level linked data from several Danish national registries were retrieved. Incidence rate per 1000 person-years (PY) was calculated. Predictors were investigated using Cox proportional hazards regression analysis. Incidence rates of having a healed wound was 236 per 1000 PY. For relapse, the incidence rate was 75 per 1000 PY, for amputation 16 per 1000 PY, and for death 100 per 1000 PY. Diabetes, peripheral arteria disease, or other comorbidities were associated with decreased chance of wound healing and increased risk of relapse, major amputation, and death. Regional differences in all four outcomes were detected. Basic or vocational education independently predicted risk of amputation and death. This study provides epidemiological data that may help identify patients at particular risk of poor outcomes. It also elucidates social inequality in outcomes.

KEYWORDS
chronic wounds, foot ulcer, major amputation, mortality, relapse

1 | BACKGROUND

Chronic leg ulceration, defined as a wound on leg or foot that does not progress through the healing process in a timely manner,\textsuperscript{1} is both a major challenge in healthcare and burdensome to affected individuals.\textsuperscript{2} This is especially true when wound treatment continues for extended periods of time and still ends in relapse, amputation, or death. Reliable epidemiological data on incidence and outcomes in patients with chronic leg ulceration is underreported,\textsuperscript{3,4} which hampers efficient resource allocation, planning, and improvement of wound care for the most affected patients.

Globally, it has been estimated that approximately 1.5 per 1000 people in the general population have a chronic leg wound (>3 weeks, all aetiologies).\textsuperscript{4} It has also been suggested that 15% to 25% of the diabetic population will have a foot wound at some point\textsuperscript{5,6} with an annual

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incidence of 2%. Although diabetic foot ulcers without complications generally heal within 6 weeks, this is not a realistic outcome for the majority of diabetic patients as only 45% of patients presenting with an initial diabetic foot ulcer will become ulcer free without experiencing amputation and alive at 12 months. There are several reasons why leg wounds do not heal spontaneously with the most common being infection, venous insufficiency, and ischaemia. These conditions are often found in combination. Critical limb threatening ischaemia has been suggested as a contributing factor for the absence of wound healing in 30% to 40% of cases and is a strong predictor of amputation and early death. In the western world, most amputations (>90%) are necessitated by complications associated with vascular disease. The majority of these patients have a history of chronic wounds.

The aim of this study was to investigate incidence and predictors of wound healing, relapse, major amputations, and/or death among patients referred to specialist treatment at hospital for chronic leg wounds.

The study was designed as an observational register-based cohort study based on nationwide individual-level linked data from several Danish national registries with 5 years of follow-up.

The study is reported in concordance with the Reporting of Studies Conducted and uses the Observational Routinely-Collected Data (RECORD) statement (an extension of the existing STROBE guidelines).

2.1 Study population

The Danish healthcare system is government funded, which ensures free access to health care at hospitals, general practitioners, and homecare for all residents. Patients with complicated leg wounds are referred to specialist treatment at hospital wound clinics while less complicated cases are treated in primary care. For this study, patients aged ≥18 years were included on their first referral to hospital for leg wounds within a 5-year period (wounds on leg or foot, all aetiologies). Patients were included if a wound required more than 6 weeks of treatment (admissions and/or outpatient visits) during the 6-year period from 1 January 2007 to 31 December 2012 (n = 8705). The index date was the date of admission/first outpatient visit plus 6 weeks. Disease-related risk factors were identified from ICD-10 codes on primary or secondary diagnoses 5 years prior to index date. Follow-up was 5 years after date of admission or until death.

A national group of wound specialists selected a comprehensive list of ICD-10 codes (supplementary appendix), which identified eligible cases of leg wounds. Other wound specialist in seven hospitals then confirmed this list. Comprehensiveness of the list was further validated by comparing codes used at two hospitals for patients with known leg wounds without more codes being identified. Pressure ulcers and cancer-related wounds were excluded as the ICD-10 codes could not definitively define whether these wounds were situated on a foot or leg. Patients were excluded if they had had major amputation within 5 years before study start (n = 243), died within 6 weeks of 1 January 2007 (n = 38) or emigrated during the study period (n = 30). The final sample for analysis consisted of 8394 patients.

2.2 Data sources

In Denmark, all residents are provided with a unique personal identification number, which is used as the key identifier in all Danish health and social care registers. Data from the following national registers were used to identify the study population and to extract data on baseline characteristics, risk factors, and outcomes:

- The Danish Civil Registration System (all persons living in Denmark).
• The Danish National Patient Register (all somatic inpatient admissions and outpatient visits including diagnosis codes).14
• The Danish National Prescription Registry (individual data on all dispensed prescription pharmaceuticals sold in Danish community pharmacies. Data consist of information on ATC codes, price, reimbursement, and so on, at patient level).15
• The Danish Population Education Register (information on completed education).16
• Different socio-economic registers from Statistics Denmark (population-level demographic data).

2.3 | Variables

2.3.1 | Outcomes

Four outcome variables were chosen for analysis: wound healing, relapse of wound, amputation, and death. Wound healing was defined as end of contact with hospital as patients are normally monitored at hospital until wound healing is achieved (wound is completely epithelised). Patients with major amputation who continued hospital contact with a wound diagnosis were not considered healed until end of contact. Relapse wound was defined as new contact with one of the abovementioned diagnoses more than 2 weeks after end of first hospital contact. Index date was last day of first hospital contact. Major amputation was defined as amputation above the ankle. Death was defined as death by all causes; see supplementary appendix for more details.

2.3.2 | Explanatory variables

The following explanatory variables were chosen based on the potential influence on extended wound healing and risk of amputation1,3,9,17:

• Age (20-year intervals [eg, 40–59])
• Sex (male/female)
• Cohabitation (cohabiting [married or residing with partner]/living alone).
• Educational level basic (primary school)/vocational (vocational or lower secondary)/higher. For each patient, the highest completed level at day of admission was selected.
• Place of residence (five regions). This variable controls for local variability in health care.
• Diabetes (yes/no). Individuals with diabetes were identified with the ICD-10 code for diabetes type 1 or 2 (E10-11) and/or having picked up prescribed antidiabetic medication from pharmacies more than once in 5 years before inclusion. To identify patients diagnosed with diabetes when they presented with a wound, individuals who had the diagnosis or had picked up prescribed antidiabetic medication from pharmacies at least once from day of admission until index date were classified as having diabetes.
• Peripheral arteria disease (PAD) (yes/no). Individuals with at least one ICD-10 code for PAD or arteriosclerosis within 5 years prior to inclusion were considered.
• Comorbidity (categorised in Charlson comorbidity index 0, 1-2, and 3+ where higher score predicted increased risk of death18). In the hazard ratio (HR) models, diagnoses of diabetes and PAD were not included in the Charlson comorbidity calculation. This was to avoid controlling for the same diagnosis multiple times as diabetes and PAD were included as separated variables in the models.

All variables were used at date of admission unless otherwise stated. More details, including diagnostic codes, are available in the supplementary appendix.

2.3.3 | Statistics

Incidence of wound healing, relapse, major amputation, and mortality were calculated as 5 years cumulated incidence among patients with chronic leg wounds (patients referred to specialist treatment at hospital for >6 weeks) and as incidence rate per 1000 person-years (PY) for both each outcome and among patients with diabetes or PAD. Characteristics of individuals are presented for all outcomes using numbers and percentages.

Cox proportional hazards regression analysis was used to estimate the effects (HRs) of covariates on the four outcomes. Results are presented as crude values and HR adjusted according to the distribution of the other covariates, 95% confidence intervals (CIs) and P values. The proportional hazard assumption was tested using Schoenfeld residuals.19 For variables that did not meet the proportional hazard assumption (cut-off value P < .01), time splitting was performed, and HR was calculated the first year and from start of years 2 to 5. All analyses were performed using Stata version 16 (StataCorp, College Station, Texas).

3 | RESULTS

The characteristics of patients referred to specialist treatment at hospital for chronic leg wounds in Denmark from 2007 to 2012 are presented in Table 1. Most patients
(76%) had basic or vocational levels of education. Within the study population, 17% had diabetes and 62% had a Charlson comorbidity index score of 0.

Of patients with chronic leg wounds, n = 7659 (91%) fulfilled the criteria for having a healed wound, and n = 91 (1%) were still in treatment for leg wounds after 5 years (Table 2). Almost one fourth of those who healed had a relapse wound. In total, n = 514 (7%) had a major amputation with 310 of these amputations happening after primary healing. Thirty-nine percent (n = 3240) died during follow-up and 630 of these died with the wound. The largest proportions of deaths occurred among the oldest and those with the most comorbidities. It is worth noting that 29% of those without registered comorbidities also died within 5 years of follow-up.

Incidence rates of a healed wound were 1812 per 1000 PY, decreasing to 1100 and 1485 PY among patients with diabetes or PAD, respectively. For relapse, the incidence rate was 75 per 1000 PY, which increased to 112 and 107 per 1000 PY among patients with diabetes or PAD, respectively. The incidence rate of amputation was 16 per 1000 PY, which increased to 27 and 66 per 1000 PY among patients with diabetes or PAD, respectively. The mortality rate was 100 per 1000 PY in the total population increasing to 104 and 184 per 1000 PY among patients with diabetes and PAD, respectively.

All four variables were found to be negatively associated with wound healing (place of residence, PAD, diabetes, and Charlson index >0) (Table 3). Place of residence and PAD did not fit the model conditions for Cox regression analysis, and time splitting was performed. It was found that place of residence (living in the Capital or Zealand regions) and PAD decreased the chance of wound healing the first year. Sex, cohabitation, and educational level did not influence chance of wound healing. A sensitivity test was performed with amputation before wound healing being put in the model as competing risk factors with only one significant change in result: older age became a predictor of lower chance of wound healing (age 80+, HR adjusted 0.89 CI 0.81–0.98, P = .01).

Six variables were found to increase the risk of relapse: older age, living alone, diabetes, PAD, and Charlson index >0 (Table 4). Age, place of residence, and diabetes did not fit the model conditions for Cox regression analysis, and time splitting was performed. Higher age and diabetes were found to increase risk of relapse independent of time splitting. Living in all regions outside the Capital region increased risk of relapse the first year. Sex and educational level did not influence risk of relapse.

All but one variable (cohabitation) was associated with major amputation within 5 years (Table 5). Time splitting was performed in three variables (sex, PAD, and Charlson index). Younger age and living in the Capital, Zealand, or Southern Denmark regions were associated with lower risk as was being female (first year only). Lower educational levels, diabetes, and particularly having PAD was associated with increased risk.

### Table 1
Characteristics of patients referred to specialist treatment at a hospital for chronic leg wounds in Denmark from 2007 to 2012

|                        | n (%)       |
|------------------------|-------------|
| Total                  | 8394 (100)  |
| Mean age (SD)          | 68.2 (17.7) |
| 18 to 39               | 612 (7)     |
| 40 to 59               | 1669 (20)   |
| 60 to 79               | 3593 (43)   |
| 80+                    | 2520 (30)   |
| Sex                    |             |
| Male                   | 4002 (48)   |
| Female                 | 4392 (52)   |
| Cohabitation           |             |
| Cohabiting             | 3839 (46)   |
| Living alone           | 4527 (54)   |
| Missing                | 28 (0)      |
| Educational level      |             |
| Basic                  | 3525 (42)   |
| Vocational             | 2820 (34)   |
| Higher                 | 1204 (14)   |
| Missing                | 845 (10)    |
| Place of residence (region) |       |
| Capital                | 2928 (35)   |
| Zealand                | 1148 (14)   |
| Southern Denmark       | 1881 (22)   |
| Central Denmark        | 1743 (21)   |
| North Denmark          | 666 (8)     |
| Missing                | 28 (0)      |
| Diabetes               | 1436 (17)   |
| Peripheral arteria disease (PAD) | 1902 (23) |
| Comorbidity (Charlson index) |    |
| 0                      | 5227 (62)   |
| 1 to 2                 | 2395 (29)   |
| ≥3                     | 772 (9)     |
| Comorbidity (Charlson modified) |     |
| 0                      | 5774 (69)   |
| 1 to 2                 | 1958 (23)   |
| ≥3                     | 662 (8)     |

*Diagnosis of diabetes and peripheral arterial disease (PAD) not included in Charlson comorbidity calculation.*
## Table 2

Five years cumulated incidence of wound healing, relapse, major amputation, and death among patients referred to specialist treatment at hospital for chronic leg wounds in Denmark from 2007 to 2012

|                          | Total n (%)<sup>a</sup> | Wound healing n (%)<sup>b</sup> | Relapse n (%)<sup>b</sup> | Major amputation n (%)<sup>b</sup> | Death n (%)<sup>b</sup> |
|--------------------------|-------------------------|---------------------------------|----------------------------|-----------------------------------|------------------------|
| **Total**                | 8394 (100)              | 7659 (91)<sup>c</sup>          | 2012 (24)                  | 514 (7)                           | 3240 (39)              |
| **Age**                  |                         |                                 |                            |                                   |                        |
| 18 to 59                 | 2281 (27)               | 2195 (96)                       | 473 (21)                   | 48 (2)                            | 218 (10)               |
| 60 to 79                 | 3593 (43)               | 3298 (92)                       | 923 (26)                   | 254 (7)                           | 1291 (36)              |
| >80                      | 2520 (30)               | 2166 (86)                       | 616 (24)                   | 212 (8)                           | 1731 (69)              |
| **Sex**                  |                         |                                 |                            |                                   |                        |
| Male                     | 4002 (48)               | 3647 (91)                       | 979 (24)                   | 270 (7)                           | 1427 (36)              |
| Female                   | 4392 (52)               | 4012 (91)                       | 1033 (24)                  | 244 (6)                           | 1813 (41)              |
| **Cohabitation**         |                         |                                 |                            |                                   |                        |
| Cohabitating             | 3839 (46)               | 3554 (93)                       | 870 (23)                   | 209 (5)                            | 1126 (29)              |
| Living alone             | 4527 (54)               | 4077 (90)                       | 1135 (25)                  | 304 (7)                            | 2111 (47)              |
| Missing                  | 28                     | 28                              | 7                         | 1                                 | 3                     |
| **Educational level**    |                         |                                 |                            |                                   |                        |
| Basic                    | 3525 (42)               | 3216 (91)                       | 916 (26)                   | 257 (7)                            | 1447 (41)              |
| Vocational               | 2820 (34)               | 2605 (92)                       | 661 (23)                   | 159 (6)                            | 883 (31)               |
| Higher                   | 1204 (14)               | 1129 (94)                       | 268 (22)                   | 43 (4)                             | 317 (26)               |
| Missing                  | 845                    | 709                             | 167                       | 55                                | 593                   |
| **Place of residence (region)** |                   |                                 |                            |                                   |                        |
| Capital                  | 2928 (35)               | 2654 (91)                       | 647 (22)                   | 150 (5)                            | 1159 (40)              |
| Zealand                  | 1148 (14)               | 1013 (88)                       | 245 (21)                   | 74 (6)                             | 414 (36)               |
| Southern Denmark         | 1881 (22)               | 1724 (92)                       | 498 (26)                   | 94 (5)                             | 758 (40)               |
| Central Denmark          | 1743 (21)               | 1603 (92)                       | 414 (24)                   | 139 (8)                            | 622 (36)               |
| North Denmark            | 666 (8)                 | 637 (96)                        | 201 (31)                   | 56 (8)                             | 284 (45)               |
| Missing                  | 28                     | 28                              | 7                         | 1                                 | 3                     |
| **Diabetes**             |                         |                                 |                            |                                   |                        |
| Yes                      | 1436 (17)               | 1244 (87)                       | 463 (32)                   | 139 (10)                           | 576 (40)               |
| **Peripheral arteria disease (PAD)** |          |                                 |                            |                                   |                        |
| Yes                      | 1902 (23)               | 1625 (85)                       | 513 (27)                   | 352 (19)                           | 1114 (59)              |
| **Charlson index**       |                         |                                 |                            |                                   |                        |
| 0                        | 5227 (62)               | 4959 (95)                       | 1152 (22)                  | 249 (5)                            | 1496 (29)              |
| 1 to 2                   | 2395 (29)               | 2093 (87)                       | 685 (29)                   | 195 (8)                            | 1199 (50)              |
| ≥3                       | 772 (9)                 | 607 (79)                        | 175 (23)                   | 70 (9)                             | 545 (71)               |
| **Charlson index modified**<sup>d</sup> |       |                                 |                            |                                   |                        |
| 0                        | 5774 (69)               | 5432 (94)                       | 1349 (23)                  | 298 (5)                            | 1663 (29)              |
| 1 to 2                   | 1958 (23)               | 1706 (87)                       | 516 (26)                   | 162 (8)                            | 1094 (56)              |
| ≥3                       | 662 (8)                 | 521 (79)                        | 147 (22)                   | 54 (8)                             | 483 (73)               |

<sup>a</sup>Column%.

<sup>b</sup>Row%.

<sup>c</sup>Including n = 190 who had a major amputation before healing and continued their hospital contact with a diagnosis of wound, n = 310 who had a major amputation after primary wound healing, and n = 2600 who died after primary healing.

<sup>d</sup>Diagnosis of diabetes and peripheral arterial disease not included in Charlson comorbidity calculation
TABLE 3  Cox regression analysis for predicting wound healing among patients referred to specialist treatment at a hospital for chronic leg wounds in Denmark from 2007 to 2012 with 5 years of follow-up

| Variable                      | Wound healing | Person-years | HR crude (95% CI) | P    | HR adjust (95% CI)<sup>a</sup> | P   |
|-------------------------------|---------------|--------------|-------------------|------|---------------------------------|-----|
| Number of subjects            |               | 7431         |                   |      |                                 |     |
| Age                           |               |              |                   |      |                                 |     |
| 18 to 39                      | 282           | 1 (Ref.)     |                   | .001 | 1 (Ref.)                        | >.10|
| 40 to 59                      | 950           | 0.88 (0.80–0.97) |            | 1.00 | (0.91–1.11)                    |     |
| 60 to 79                      | 1940          | 0.84 (0.77–0.92) |            | 1.01 | (0.92–1.10)                    |     |
| 80+                           | 1054          | 0.90 (0.82–0.99) |            | 1.05 | (0.95–1.16)                    |     |
| Sex                           |               |              |                   | .003 |                                 | >.10|
| Male                          | 2152          | 1 (Ref.)     |                   |      | 1 (Ref.)                        |     |
| Female                        | 2074          | 1.07 (1.02–1.12) |            | 0.99 | (0.94–1.04)                    |     |
| Cohabitation                  |               |              |                   | >.10 |                                 | >.10|
| Cohabitating                  | 2014          | 1.01 (0.97–1.06) |            | 1.00 | (0.95–1.05)                    |     |
| Living alone                  | 2194          | 1 (Ref.)     |                   |      |                                 |     |
| Educational level             |               |              |                   | .01  |                                 | >.10|
| Basic                         | 1684          | 1.08 (1.01–1.16) |            | 1.04 | (0.97–1.11)                    |     |
| Vocational                    | 1523          | 1.01 (0.94–1.08) |            | 1.01 | (0.94–1.09)                    |     |
| Higher                        | 668           | 1 (Ref.)     |                   |      |                                 |     |
| Place of residence (region)   |               |              |                   | <.001|                                 | <.001|
| Capital                       | 1828          | 1 (Ref.)     |                   | 1.05 | (0.96–1.14)                    |     |
| Zealand                       | 769           | 1.02 (0.94–1.10) |            | 1.05 | (0.96–1.14)                    |     |
| Southern Denmark              | 669           | 1.49 (1.39–1.59) |            | 1.47 | (1.37–1.58)                    |     |
| Central Denmark               | 737           | 1.41 (1.32–1.50) |            | 1.40 | (1.30–1.50)                    |     |
| North Denmark                 | 206           | 1.90 (1.73–2.08) |            | 1.88 | (1.70–2.07)                    |     |
| Place of residence (region)   |               |              |                   | <.001|                                 | .02 |
| Capital                       | 1 (Ref.)      |              |                   | 1.09 |                                 |     |
| Zealand                       | 769           | 0.75 (0.60–0.89) |            | 0.81 | (0.65–0.97)                    |     |
| Southern Denmark              | 669           | 1.26 (1.00–1.52) |            | 1.22 | (0.96–1.48)                    |     |
| Central Denmark               | 737           | 1.03 (0.83–1.23) |            | 1.09 | (0.88–1.31)                    |     |
| North Denmark                 | 206           | 0.98 (0.62–1.34) |            | 0.96 | (0.59–1.33)                    |     |
| Diabetes                      |               |              |                   | <.001|                                 | <.001|
| No                            | 3095          | 1 (Ref.)     |                   | 1.07 | (0.63–0.72)                    |     |
| Yes                           | 1131          | 0.67 (0.63–0.71) |            | 0.67 | (0.63–0.72)                    |     |
| PAD                           |               |              |                   | <.001|                                 | <.001|
| No                            | 3132          | 1 (Ref.)     |                   | 1.09 |                                 |     |
| Yes                           | 1094          | 0.73 (0.69–0.78) |            | 0.71 | (0.67–0.76)                    |     |
| Charlson index modified<sup>b</sup> |           |         |                   | .01  |                                 | .01 |
| 0                             | 2924          | 1 (Ref.)     |                   |     |                                 |     |
| 1 to 2                        | 973           | 0.93 (0.88–0.99) |            | 0.94 | (0.89–1.00)                    |     |
| ≥3                            | 330           | 0.85 (0.77–0.93) |            | 0.88 | (0.80–0.97)                    |     |

Abbreviation: PAD, peripheral artery disease.

<sup>a</sup> All HR adjusted for the listed covariates.

<sup>b</sup> Charlson index excluding diabetes and peripheral arterial disease.

<sup>c</sup> Timesplitting, HR the first year and from start of year 2 until end of year 5.
Table 4  Cox regression analysis for predicting relapse, among patients referred to specialist treatment at a hospital for chronic leg wounds in Denmark from 2007 to 2012 within 5 years of follow-up

| Variable | Relapse | Person-years | HR crude (95% CI) | P | HR adjust (95% CI) a | P |
|----------|---------|--------------|------------------|---|---------------------|---|
| Number of subjects | | 7441 |
| Age | | | | | | |
| 18 to 39 | | 2757 | 0.42 (0.30–0.61) | <.001 | 0.51 (0.35–0.74) | <.001 |
| 40 to 59 | | 6422 | 0.71 (0.58–0.87) | <.001 | 0.81 (0.65–1.00) | <.001 |
| 60 to 79 | | 11 843 | 0.83 (0.71–0.98) | <.001 | 0.83 (0.70–0.99) | <.001 |
| 80+ | | 5984 | 1 (Ref.) | 1 (Ref.) | 1 (Ref.) | 1 (Ref.) |
| Age | | | | | | |
| 18 to 39 | | | 0.09 (0.06–0.11) | <.001 | 0.29 (0.19–0.39) | <.001 |
| 40 to 59 | | | 0.62 (0.52–0.72) | <.001 | 0.69 (0.56–0.81) | <.001 |
| 60 to 79 | | | 0.78 (0.67–0.88) | <.001 | 0.78 (0.66–0.90) | <.001 |
| 80+ | | | 1 (Ref.) | 1 (Ref.) | 1 (Ref.) | 1 (Ref.) |
| Sex | | | | >.10 | >.10 |
| Male | | 13 022 | 1 (Ref.) | 1 (Ref.) | 1 (Ref.) | 1 (Ref.) |
| Female | | 13 985 | 0.98 (0.89–1.07) | <.001 | 0.93 (0.84–1.03) | <.001 |
| Cohabitation | | | | <.001 | <.001 |
| Cohabiting | | 13 320 | 0.81 (0.74–0.88) | <.001 | 0.84 (0.76–0.92) | <.001 |
| Living alone | | 13 581 | 1 (Ref.) | 1 (Ref.) | 1 (Ref.) | 1 (Ref.) |
| Educational level | | | | <.001 | >.10 |
| Basic | | 10 947 | 1.33 (1.16–1.53) | <.001 | 1.12 (0.98–1.29) | <.001 |
| Vocational | | 9697 | 1.10 (0.96–1.27) | <.001 | 1.05 (0.91–1.21) | <.001 |
| Higher | | 4380 | 1 (Ref.) | 1 (Ref.) | 1 (Ref.) | 1 (Ref.) |
| Place of residence (region) | | | | <.001 | <.001 |
| Capital | | 9655 | 1 (Ref.) | 1 (Ref.) | 1 (Ref.) | 1 (Ref.) |
| Zealand | | 3698 | 1.37 (1.07–1.75) | <.001 | 1.38 (1.06–1.78) | <.001 |
| Southern Denmark | | 5868 | 2.11 (1.75–2.55) | <.001 | 2.27 (1.86–2.78) | <.001 |
| Central Denmark | | 5699 | 1.69 (1.38–2.07) | <.001 | 1.77 (1.43–2.20) | <.001 |
| North Denmark | | 1980 | 2.50 (1.96–3.18) | <.001 | 2.43 (1.87–3.16) | <.001 |
| Place of residence (region) | | | | .05 | >.10 |
| Capital | | 1 (Ref.) | 1 (Ref.) | 1 (Ref.) | 1 (Ref.) | 1 (Ref.) |
| Zealand | | 0.84 (0.69–1.00) | 0.84 (0.68–1.00) | 0.84 (0.68–1.00) | 0.84 (0.68–1.00) |
| Southern Denmark | | 0.91 (0.77–1.05) | 0.94 (0.79–1.09) | 0.94 (0.79–1.09) | 0.94 (0.79–1.09) |
| Central Denmark | | 0.85 (0.72–0.99) | 0.90 (0.75–1.04) | 0.90 (0.75–1.04) | 0.90 (0.75–1.04) |
| North Denmark | | 1.09 (0.85–1.32) | 1.07 (0.83–1.32) | 1.07 (0.83–1.32) | 1.07 (0.83–1.32) |
| Diabetes | | | | <.001 | <.001 |
| No | | 22 879 | 1 (Ref.) | 1 (Ref.) | 1 (Ref.) | 1 (Ref.) |
| Yes | | 4128 | 1.37 (1.16–1.62) | <.001 | 1.39 (1.17–1.66) | <.001 |
| Diabetes | | | | <.001 | <.001 |
| No | | 1 (Ref.) | 1 (Ref.) | 1 (Ref.) | 1 (Ref.) | 1 (Ref.) |
| Yes | | 1.81 (1.57–2.05) | 1.74 (1.49–1.98) | <.001 | 1.74 (1.49–1.98) | <.001 |
| PAD | | | | <.001 | <.001 |
| No | | 22 201 | 1 (Ref.) | 1 (Ref.) | 1 (Ref.) | 1 (Ref.) |

(Continues)
TABLE 4  (Continued)

| Variable                | Relapse | Person-years | HR crude (95% CI) | P     | HR adjust (95% CI) | P     |
|-------------------------|---------|--------------|-------------------|-------|-------------------|-------|
| Yes                     | 4806    | 1.51 (1.36–1.67) | <.001             | 1.32 (1.18–1.47) | <.001 |
| Charlson index modifiedb|         |              |                   |       |                   |       |
| 0                       | 20 407  | 1 (Ref.)     |                   |       | 1 (Ref.)          |       |
| 1 to2                   | 5235    | 1.42 (1.28–1.57) | <.001             | 1.34 (1.21–1.49) |       |
| ≥3                      | 1365    | 1.50 (1.26–1.77) | <.001             | 1.30 (1.09–1.56) |       |

Abbreviation: PAD, peripheral artery disease.

*aAll HRs are adjusted for the listed covariates.

bCharlson index modified with diagnosis of diabetes and peripheral arterial disease not included in calculation.

cTimesplitting, HR the first year and from start of year 2 until end of year 5.

TABLE 5  Cox regression analysis for predicting amputations among patients referred to specialist treatment at a hospital for chronic leg wounds in Denmark from 2007 to 2012 within 5 years of follow-up

| Variable                | Major amputation | Person-years | HR crude (95% CI) | P     | HR adjust (95% CI) | P     |
|-------------------------|------------------|--------------|-------------------|-------|-------------------|-------|
| Number of subjects      | 7528             |              |                   | <.001 |                   | <.001 |
| Age                     |                  |              |                   | <.001 |                   | <.001 |
| 18 to 39                | 3021             | 0.03 (0.01–0.11) | <.001             | 0.04 (0.01–0.29) | <.001 |
| 40 to 59                | 7666             | 0.24 (0.18–0.34) | <.001             | 0.42 (0.29–0.60) | <.001 |
| 60 to 79                | 13 816           | 0.70 (0.58–0.84) | <.001             | 0.76 (0.62–0.93) | <.001 |
| 80+                     | 6901             | 1 (Ref.)     |                   | 1 (Ref.) |                   |       |
| Sex                     |                  |              |                   |       |                   |       |
| Male                    | 15 233           | 1 (Ref.)     | <.001             | 1 (Ref.) | <.001             |       |
| Female                  | 16 171           | 0.73 (0.58–0.90) | <.001             | 0.73 (0.57–0.93) | <.001 |
| Sex                     |                  |              |                   | >.1   |                   | >.1   |
| Male                    |                  | 1 (Ref.)     |                   | 1 (Ref.) |                   |       |
| Female                  |                  | 1.03 (0.74–1.32) | >.1   | 1.03 (0.71–1.34) | >.1   |
| Cohabitation            |                  |              |                   | <.002 |                   | .06   |
| Cohabiting              | 15 476           | 0.76 (0.63–0.90) | <.001             | 0.83 (0.68–1.01) | <.001 |
| Living alone            | 15 800           | 1 (Ref.)     |                   | 1 (Ref.) |                   |       |
| Educational level       |                  |              |                   | <.001 |                   | .05   |
| Basic                   | 12 869           | 2.20 (1.59–3.04) | <.001             | 1.50 (1.08–2.09) | <.001 |
| Vocational              | 11 262           | 1.63 (1.16–2.28) | <.001             | 1.40 (0.99–1.96) | <.001 |
| Higher                  | 5061             | 1 (Ref.)     |                   | 1 (Ref.) |                   | <.001 |
| Place of residence (region) |              |              |                   | <.001 |                   | .008  |
| Capital                 | 10 996           | 1 (Ref.)     | <.001             | 1 (Ref.) |                   |       |
| Zealand                 | 4308             | 1.27 (0.96–1.68) | <.001             | 1.13 (0.84–1.52) | <.001 |
| Southern Denmark        | 7004             | 0.97 (0.75–1.26) | <.001             | 1.02 (0.77–1.34) | <.001 |
| Central Denmark         | 6581             | 1.55 (1.23–1.96) | <.001             | 1.52 (1.19–1.95) | <.001 |
| North Denmark           | 2386             | 1.67 (1.22–2.27) | <.001             | 1.31 (0.94–1.85) | <.001 |
| Diabetes                |                  |              |                   | <.001 |                   | <.001 |
| No                      | 26 165           | 1 (Ref.)     | <.001             | 1 (Ref.) | <.001             | <.001 |
### Table 5 (Continued)

| Variable | Major amputation | Person-years | HR crude (95% CI) | P   | HR adjust (95% CI)<sup>a</sup> | P   |
|----------|------------------|--------------|-------------------|-----|-------------------------------|-----|
| Yes      |                  | 5240         | 1.80 (1.48–2.19)  | .01 | 1.72 (1.39–2.13)              | .01 |
| PAD      |                  |              |                   |     |                               |     |
| No       |                  | 26 104       | 1 (Ref.)          |     | 1 (Ref.)                      |     |
| Yes      |                  | 5301         | 13.35 (10.27–17.36) | <.001 | 10.13 (7.62–13.48)          | <.001 |
| PAD      |                  |              |                   |     |                               |     |
| No       |                  |              |                   |     |                               |     |
| Yes      |                  |              |                   |     |                               |     |
| Charlson index modified<sup>b</sup> |                  |              |                   |     |                               |     |
| 0        |                  | 23 654       | 1 (Ref.)          |     | 1 (Ref.)                      |     |
| 1 to 2   |                  | 6167         | 1.75 (1.37–2.23)  | .001 | 1.32 (1.02–1.71)              | .001 |
| ≥3       |                  | 1584         | 2.16 (1.53–3.05)  |     | 1.38 (0.95–2.00)              |     |
| Charlson index modified<sup>b</sup> |                  |              |                   |     |                               |     |
| 0        |                  |              |                   |     |                               |     |
| 1 to 2   |                  |              |                   |     |                               |     |
| ≥3       |                  |              |                   |     |                               |     |

Abbreviation: PAD, peripheral artery disease.

<sup>a</sup>All HRs are adjusted for the listed covariates.

<sup>b</sup>Charlson index modified with diagnosis of diabetes and peripheral arterial disease not included in calculation.

<sup>c</sup>Timesplitting, HR the first year and from start of year 2 until end of year 5.

### Table 6 Cox regression analysis for predicting death among patients referred to specialist treatment at a hospital for chronic leg wounds in Denmark from 2007 to 2012 within 5 years of follow-up

| Variable | Death | Person-years | HR crude (95% CI) | P   | HR adjust (95% CI)<sup>a</sup> | P   |
|----------|-------|--------------|-------------------|-----|-------------------------------|-----|
| Number of subjects |       | 7534         |                   |     |                               |     |
| Age      |       |              |                   |     |                               |     |
| 18 to 39 |       | 3026         | 0.01 (0.01–0.03)  | <.001 | 0.02 (0.01–0.05)              | <.001 |
| 40 to 59 |       | 7782         | 0.11 (0.10–0.13)  |     | 0.17 (0.14–0.20)              |     |
| 60 to 79 |       | 14 382       | 0.38 (0.36–0.41)  |     | 0.46 (0.42–0.50)              |     |
| 80+      |       | 7262         | 1 (Ref.)          |     | 1 (Ref.)                      |     |
| Sex      |       |              |                   |     |                               |     |
| Male     |       | 15 804       | 1 (Ref.)          |     | 1 (Ref.)                      |     |
| Female   |       | 16 648       | 1.20 (1.12–1.29)  |     | 0.77 (0.71–0.83)              |     |
| Cohabitation |       |              |                   |     |                               |     |
| Cohabiting |     | 15 906       | 0.56 (0.52–0.60)  | <.001 | 0.77 (0.71–0.84)              | <.001 |
| Living alone |   | 16 415       | 1 (Ref.)          |     | 1 (Ref.)                      |     |
| Educational level |       |              |                   |     |                               |     |
| Basic    |       | 13 410       | 1.74 (1.54–1.96)  | <.001 | 1.20 (1.06–1.36)              | .01  |
| Vocational |    | 11 600       | 1.23 (1.08–1.40)  |     | 1.12 (0.99–1.28)              |     |
| Higher   |       | 5145         | 1 (Ref.)          |     | 1 (Ref.)                      |     |
| Place of residence (region) |       | Year 1<sup>c</sup> | .006 | Year 1<sup>c</sup> | .002 |

(Continues)
Two variables needed time splitting to fit the assumptions for Cox regression analysis on risk of death (place of residence and Charlson index) (Table 6). Younger age, female, living with someone, and residing in the Capital or Central Denmark (first year) were protective factors from death. Lower educational level, diabetes, PAD, and especially more comorbidities (Charlson index > 0) increased risk of dying within 5 years from presenting with a leg wound that was not healed within 6 weeks.

| Variable            | Death Person-years | HR crude (95% CI) | \( P \) | HR adjust (95% CI)\(^a\) | \( P \) |
|--------------------|-------------------|------------------|--------|---------------------------|--------|
| Capital            | 11 302            | 1 (Ref.)         |        | 1 (Ref.)                  |        |
| Zealand            | 4458              | 1.07 (0.89–1.30) | 1.24   | 1.24 (1.00–1.54)          | .006   |
| Southern Denmark   | 7197              | 1.03 (0.88–1.22) | 1.24   | 1.24 (1.03–1.49)          | .006   |
| Central Denmark    | 6859              | 1.00 (0.84–1.18) | 1.05   | 1.05 (0.86–1.28)          | .006   |
| North Denmark      | 2504              | 1.12 (0.89–1.41) | 1.29   | 1.29 (1.00–1.68)          | .006   |

Place of residence (region) Years 2 to 5\(^e\) \( P \) Years 2 to 5\(^e\) \( P \)

| Capital         | 1 (Ref.)         | 1 (Ref.)       |        |        |
| Zealand         | 0.83 (0.72–0.95) | 0.91 (0.77–1.05) |        |        |
| Southern Denmark| 1.02 (0.91–1.14) | 1.14 (1.00–1.28) |        |        |
| Central Denmark | 0.84 (0.74–0.94) | 0.92 (0.80–1.04) |        |        |
| North Denmark   | 1.10 (0.92–1.27) | 1.17 (0.96–1.37) |        |        |

Diabetes         >.10 \( P \) >.10 \( P \)

| No   | 26 924 | 1 (Ref.) | 1 (Ref.) |        |        |
|------|-------|---------|---------|--------|--------|
| Yes  | 5527  | 1.05 (0.96–1.15) | 1.13 (1.02–1.25) |        |        |

PAD \( P \) \( P \)

| No   | 26 406 | 1 (Ref.) | 1 (Ref.) |        |        |
|------|-------|---------|---------|--------|--------|
| Yes  | 6046  | 2.24 (2.08–2.41) | 1.63 (1.50–1.76) |        |        |

Charlson index modified\(^b\) Year 1\(^c\) \( P \) Year 1\(^c\) \( P \)

| 0    | 24 350 | 1 (Ref.) | 1 (Ref.) |        |        |
|------|-------|---------|---------|--------|--------|
| 1 to 2 | 6450  | 2.80 (2.45–3.20) | 2.51 (2.15–2.94) |        |        |
| ≥3   | 1651  | 5.01 (4.26–5.89) | 4.70 (3.92–5.64) |        |        |

Charlson index modified\(^b\) Years 2 to 5\(^e\) \( P \) Years 2 to 5\(^e\) \( P \)

| 0    | 1 (Ref.) | 1 (Ref.) |        |        |
|------|---------|---------|--------|--------|
| 1 to 2 | 2.29 (2.08–2.50) | 2.00 (1.80–2.21) |        |        |
| ≥3   | 3.65 (3.16–4.13) | 3.16 (2.71–3.61) |        |        |

Abbreviation: PAD, peripheral arteria disease.

\(^a\)All HRs are adjusted for the listed covariates.

\(^b\)Charlson index modified with diagnosis of diabetes and peripheral arterial disease not included in calculation.

\(^c\)Timesplitting, HR the first year and from start of year 2 until end of year 5.

4 | DISCUSSION

This study identified patients with chronic leg wounds at risk of delayed wound healing, relapse, major amputation, and death. It confirms that PAD is a strong predictor of amputation and death\(^10\) as are diabetes and having more comorbidities (Charlson index > 0). The finding of significant differences in all outcomes associated with place of residence and the higher risk of major amputations and death associated with lower educational level and living alone is surprising.

4.1 | Wound healing

Comparable to other wound healing studies,\(^20,21\) 91% of patients experienced a healed wound during follow-up. However, 1% still had an unhealed wound after 5 years, and diabetes was particularly associated with decreased
chance of wound healing. A list of factors is known to predict healing in chronic wounds. This list includes renal disease, wound aetiology, and malnutrition among others. Although highly relevant, detailed data on more predicting factors are not routinely registered and was therefore not available for this study. Future benchmarking efforts that implement clinical wound care data registries in Denmark would be beneficial.

Patients whose wounds do not heal or for whom healing would pose an undue medical or social burden should be involved in shared decision-making processes regarding whether they prefer a palliative approach to wound care that reduces the complexity of care and minimises risk of infection and hospitalisation, or if they prefer a major amputation.

4.2 | Relapse

The cumulative incidence for relapse was 24% in the total population of patients with chronic leg wounds. This increased to 32% and 27% among patients with diabetes or PAD, respectively. A European recurrence rate of diabetic foot ulcers of 24.9% per PY was calculated in a recent systematic review and meta-analysis of 49 studies (9670.6 PY of follow-up). Relapse has been estimated to occur in 65% of cases among patients with diabetic foot ulcers within 5 years. This number was 17% to 20% within 12 months among patients with venous leg ulcers. These studies did not include only patients with chronic leg wounds as ours did, and our rates of relapse could be underestimated if the relapse wound did not warrant hospital contact. Patient education and access to appropriate footwear combined with other preventive interventions tailored to the needs of patients most at risk are crucial for preventing recurrent leg wounds regardless of aetiology. The regional differences we observed could indicate differences in access to these preventive interventions. It is important to note that differences in study design and populations make comparisons difficult.

4.3 | Major amputation

Our observation of regional differences confirms variations in amputation rates, which has been seen in studies between and within countries (ie, some countries have shown larger rates than others). It is important to acknowledge that amputation is not a measure of the natural history of disease but simply a treatment and that the selection of treatment varies according to healthcare provider, medical necessity, medical need, and patient preference.

4.4 | Risk of death

This study emphasises that patients with chronic leg wounds are in the latter part of their lives. In total, 39% of all cases died within 5 years. The proportion of those with PAD was 59% and as high as 73% among the patients with multiple comorbidities (Charlson comorbidity index ≥3). In comparison, 4-year mortality rates of 19% to 64% have been reported among patients with PAD depending on severity and whether or not they have wounds. Additionally, 5-year mortality rates of 46% have been reported among patients with diabetic foot ulcers who are treated in specialist diabetes centres. Although it has been shown that having diabetes and foot ulcer increases risk of death, this study identified no literature describing the same association in patients with leg wounds and other comorbidities. This could be a topic for future research.

4.5 | Inequality in health

Our findings point at more areas of inequalities in health among patients with chronic leg wounds. Current evidence supports an association between socioeconomic inequalities and non-communicable diseases globally. Although evidence is incomplete and limited, this has become even more evident during the Covid-19 pandemic. Even though Denmark is a small country with free health care available to all residents, studies have found that the country has socioeconomic inequalities in health that are among the highest of the Nordic countries and that these inequalities have increased over time.

Lower education has recently been associated with both higher morbidity and inadequate health literacy. Lower educational level and living alone, for example, have been associated with lower adherence to evidence-based practice in heart failure care. Regional differences in outcomes could indicate local differences in care provided. This may translate into differences in access to vascular surgery and underuse of evidence-based practices in wound care, which was seen in another study.

4.6 | Strengths and limitations

To our knowledge, this is the first study to investigate incidence and predictors of wound healing, relapse,
major amputations, and/or death among patients with chronic leg wounds who are referred to specialist treatment at hospital with 5 years of follow up and is based on nationwide register data. The major strength of the study is the nationwide comprehensive prospectively collected data of a list of clinically relevant factors with potential influence on outcomes in patients with chronic wounds. These factors included reliable data on diabetes and social characteristics. Another strength of this study is that there is little missing data and relatively long follow-up period.

This study is limited by the fact that available wound diagnoses did not make it possible to differentiate patients into individuals with venous, arterial, or diabetic ulcers. This lack of classification makes it difficult to compare our findings with other studies in this particular stratification. We report outcomes for all patients with chronic leg wounds who have a number of epidemiological characteristics, which have a clear impact on outcomes. Our results may help identify patients at particular risk of poor outcomes independent of wound aetiology. Even though this study is based on nationwide data, it does not represent all patients with chronic wounds in Denmark as there may be patients who were not referred to hospital for wound management. By defining wound healing as end of contact with the hospital, we might overestimate healing rates as some patients might be released from hospital before wound healing occurs.

5 | CONCLUSION

This study provides reliable epidemiological data on four clinically important outcomes and is based on a group of patients who were seeking medical care, which is by definition the group of patients health care can treat. Our estimates are directly applicable to patients with chronic leg wounds who are receiving care at specialist wound care facilities and for whom new treatments and preventive, rehabilitative, and palliative strategies can be introduced.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data underlying this article are available in the article. Raw data cannot be shared for privacy reasons. Programming codes will be shared on reasonable request to the corresponding author.

ETHICS STATEMENT

The study was approved by the Danish Data Protection Agency, J.nr. 19/10332. When conducting registry-based research in Denmark, no further approval is required.

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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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