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Ulcerative complications in diabetics with onychomycosis in primary care

A longitudinal cohort study in Dutch general practice

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Abstract

Introduction: Diabetic foot ulcers are feared complications of diabetes mellitus, requiring extensive treatment and hospital admissions, ultimately leading to amputation and increased mortality. Different factors contribute to the development of foot ulcers and related complications. Onychomycosis, being more prevalent in diabetics, could be an important risk factor for developing ulcers and related infections. However, the association between onychomycosis and diabetic complications has not been well studied in primary care.

Research Design and Methods: To determine the impact of onychomycosis on ulcer development and related complications in diabetic patients in primary care, a longitudinal cohort study was carried out using routine care data from the Extramural LUMC Academic Network (ELAN). Survival analyses were performed through Cox proportional hazards models with time-dependent covariates.

Results: Data from 48,212 patients with a mean age of 58 at diagnosis of DM, predominantly type 2 (87.8%), were analyzed over a median follow-up of 10.3 years. 5.7% of patients developed an ulcer. Onychomycosis significantly increased the risk of ulcer development (HR 1.37, 95% CI 1.13 - 1.66), not affected by antimycotic treatment, nor after adjusting for confounders (HR 1.23, 95% CI 1.01-1.49). The same was found for surgical interventions (HR 1.54, 95% CI 1.35-1.75) and skin infections (HR 1.48, CI 95% 1.28-1.72), again not affected by treatment and significant after adjusting for confounders (HR 1.32, 95% CI 1.16-1.51 and HR 1.27, 95% CI 1.10-1.48, respectively).

Conclusions: Onychomycosis significantly increased the risk of ulcer development in patients with DM in primary care, independently of other risk factors. In addition, onychomycosis increased the risk of surgeries and infectious complications. These results underscore the importance of giving sufficient attention to onychomycosis in primary care and corresponding guidelines. Early identification of onychomycosis during screening and routine care provides a good opportunity for timely recognition of increased ulcer risk.

Keywords: *Onychomycosis, Diabetes Mellitus, Diabetic Foot, Ulcer, Cox Proportional-Hazards*

Key message

What is already known: Onychomycosis has been shown to be significantly associated with ulcer development in diabetic patients. However, this evidence originated from non-primary care data.

What this study adds: This large cohort study shows that onychomycosis is significantly and independently associated with ulcer development in diabetic patients in primary care.

How this study might affect research, practice, or policy: Our findings support the clinical relevance of onychomycosis, emphasizing the importance of recognizing fungal toenail infections during routine primary care for diabetic patients.

Introduction

According to the International Diabetes Federation, an estimated 537 million people worldwide suffer from diabetes mellitus (DM) [1]. In 2019, 1.1 million diabetic patients were registered in Dutch primary care, about 7% of the adult population [2]. Complications of DM are the cause of significant morbidity and medical costs [3,4]. With the prevalence of DM projected to continue to rise, prevention and management of diabetic complications are becoming increasingly important [2].

One of the most feared complications of DM is the diabetic foot, which includes diabetic foot ulcers [5]. Ulcers often require extensive treatment and hospitalization, and can ultimately lead to lower extremity amputation [6,7]. To prevent ulcer development and its consequences, early recognition of patients at risk is essential [8].

Various risk factors for ulcer development have been identified. The most prominent are prior ulcer or amputation, neuropathy, foot deformity, focal pressure points, and peripheral arterial disease [9,10]. Furthermore, male gender, signs of microangiopathy, including visual impairment, suboptimal glycemic control (i.e. elevated HbA1c levels), insulin therapy, and onychomycosis were identified as additional significant risk factors [11-13].

Regarding the latter, diabetic patients are more prone to fungal infections in general and onychomycosis in particular: up to one-third of diabetic patients are estimated to have onychomycosis compared to 4.3% in the general population [14,15]. Although onychomycosis is often considered a nuisance and unesthetic at most, numerous studies have shown onychomycosis to have a substantial negative effect on the quality of life and predispose patients to complications such as bacterial infections, especially in diabetic patients [16-18]. Although previous studies suggest onychomycosis may be an important risk factor for ulcer development, this relationship has not been well studied in primary care [9,19-22].

The aim of this study was to assess if onychomycosis, treated or not, is a risk factor for diabetic foot ulcers, and secondly, for related complications in primary care. Therefore, we conducted a longitudinal cohort study using routine-care data of diabetic patients from primary care.

Methods

Study design

This study was designed as a longitudinal cohort using routine-care data from primary care patients with DM. The date of diagnosis of DM was considered the start of follow-up; the end of follow-up was either development of an outcome, date of death, deregistration or data extraction. Using pre-defined risk factors, primarily onychomycosis and secondarily antimycotic treatment and related, often underlying conditions, both exposed and unexposed individuals were identified. Following patients forward in time, the incidences of the outcomes of interest were compared between the two groups [23]. Ulcer development was considered the primary outcome; hospital referrals, surgical interventions (performed within primary care), and the bacterial skin infections cellulitis and erysipelas, were secondary outcomes.

Data and setting

Routine-care data from primary care practices affiliated with the Extramural LUMC (Leiden University Medical Center) Academic Network (ELAN) were used. ELAN is a collaboration between Dutch general practitioners and the Department of Public Health and Primary Care (PHEG) from the LUMC, in the western part of the Netherlands. ELAN periodically extracts and stores these data in their data-warehouse and provides controlled access to these data while safeguarding privacy and conforming to all applicable laws and regulations [24,25]. The data used for this study were extracted on May 11th, 2022.

Participants

The records of all diabetic patients, regardless of subtype, were extracted. Based on the intended analyses, patient records meeting the following criteria were selected:

1. Date of diagnosis of DM recorded
2. Age between 0-100
3. Date of exposure (risk factor) and event (complication) recorded, i.e. time between diagnosis of DM and exposure or outcome of interest known

4. Exposure or event occurred after diagnosis of DM and before deregistration, death or data extraction, i.e. during follow-up

Regarding the latter, since the start of follow-up was defined as the date on which the diagnosis of DM was established, only exposures and events occurring after baseline were used for analyses.

Patient and Public Involvement

It was not appropriate to involve patients or the public in the design, conduct, reporting, or dissemination plans of our research.

Measurements and Outcomes

Regarding exposures and outcome measures, the diagnoses and comorbidities extracted were coded using the International Classification of Primary Care (ICPC) coding system and their corresponding dates of registration. Similarly, data on medication, referrals, and interventions were extracted using their corresponding coding systems.

Besides onychomycosis, the available risk factors of interest were tinea pedis, peripheral artery disease, venous insufficiency, ankle edema, psoriasis, lichen planus, eczema, neuropathy, smoking, and antimycotic treatment. In addition, age and sex were also considered potential confounders and used for analyses.

Our primary outcome measure was ulcer development. Secondary outcome measures were hospital referrals, surgical interventions performed within primary care, i.e. minor procedures such as debridement, and infectious complications (cellulitis and erysipelas). Only hospital referrals related to DM referring to surgery, internal medicine or dermatology, were used for analyses.

Cellulitis and erysipelas, although coded differently, were combined since both entities are used interchangeably. The same was done for ulcus cruris and diabetic foot ulcers, combining them into a single variable for ulcers. In case two variables were combined and a patient was diagnosed with having both, the diagnosis that occurred first, i.e. with the shortest time to diagnosis of DM, was used for analysis.

Statistical analyses

Descriptive statistics were used to analyze patient characteristics at baseline and to describe the occurrence of both exposures and outcomes during follow-up.

Since exposures and outcomes of interest were not constant over time, i.e. occurring at different moments during follow-up, these were considered to be time-dependent. Therefore, to answer our research questions, Cox-proportional hazards models using time-dependent covariates were required, thus using the time between baseline and diagnosis of an exposure or event. The proportional hazard (PH) assumption was checked by testing whether the covariates interacted significantly with time. In case of violation, the corresponding hazard ratio (HR) was modelled as a time-dependent effect by including an interaction term between the logarithm of time and the covariate.

First, the association between onychomycosis and ulcer development was evaluated as single predictor (univariate model), then adjusted for antimycotic treatment (first multivariate model), and finally for all potential confounders mentioned above (second multivariate model). The proportional hazards assumption (PH) was violated for age and neuropathy in the last model, corrected for by including the interaction terms with the logarithm of time in the corresponding model.

Regarding secondary outcomes, the associations between onychomycosis and hospital referrals, surgeries, and bacterial skin infections were evaluated using a similar set of uni- and multivariate models to adjust for antimycotic treatment and for all confounders combined. Again, the interaction terms with the logarithm of time were used for the covariates for which the PH-assumption was violated. These were neuropathy and smoking in the final multivariate model for hospital referrals, age and ankle edema in the final model for surgical interventions, and age in the final model for bacterial skin infections.

P-values of <0.05 were considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics (Version 28).

Results

Patient characteristics

The initial data extraction consisted of 50,292 patient records. After applying the criteria as described, 48,212 records were selected for analysis. Patient characteristics are shown in Table 1. Our sample included 22,877 women (47.5%) and 25,335 men (52.5%). The mean age at baseline was 58.3 years (SD 15.7). The vast majority of patients (87.8%) were diagnosed with type 2 DM; only 6.5% had type 1 DM and the remaining cases (5.7%) were unspecified.

Table 1. Patient characteristics	
Patients, total (N)	48,212
Mean age at onset of DM in years (SD)	58.3 (15.7)
Gender, N (%)	
Male	25,335 (52.5)
Female	22,877 (47.5)
Type of Diabetes Mellitus, N (%)	
Type 1	3,131 (6.5)
Type 2	42,312 (87.8)
Unspecified	2,769 (5.7)

Table 1. Patient characteristics at baseline i.e. start of follow-up.

The median follow-up time was 10.3 years (IQR 10.8). Exposures and events recorded during follow-up are presented in Table 2.

The cumulative incidence of onychomycosis in our sample was 4.1%. Regarding the other exposures, ankle edema (13.5%) and eczema (12.2%) were most frequently recorded. During follow-up, 6.2% of patients received any form of antimycotic treatment. In total 2,771 patients (5.7%) developed an ulcer after a median of 8.8 years (IQR 9.6). Regarding the secondary outcomes, surgical interventions occurred most frequently (12.8%) after a median of 7.8 years (IQR 8.9), followed by infections (10.1%) after a median 7.7 years (IQR 9.4). 6.3% needed a hospital referral after a median of 7.4 years (IQR 9.2).

Table 2. Exposures and events during follow-up	
	N (cumulative incidence, %)
Total cohort	48,212
Exposures	
Onychomycosis	1,959 (4.1)
Tinea pedis	2,006 (4.2)
Peripheral arterial disease	2,381 (4.9)
Venous insufficiency	275 (0.6)
Ankle edema	6,494 (13.5)
Psoriasis	1,193 (2.5)
Lichen ruber planus	166 (0.3)
Eczema	5,870 (12.2)
Neuropathy	3,287 (6.8)
Smoking	2,930 (6.1)
Antimycotic treatment	
Any type	3,005 (6.2)
Local	2,777 (5.8)
Systemic	228 (0.5)
Events	
Ulcer	2,771 (5.7)
Cellulitis/erysipelas	4,889 (10.1)
Hospital referral	3,060 (6.3)
Surgical intervention	6,149 (12.8)

Table 2. Overview of exposures and events during follow-up.

Primary outcome: ulcer development

The results for the association between onychomycosis and ulcer development are shown in Table 3. In univariate analysis, onychomycosis was significantly associated with ulcer development (HR 1.37, 95% CI 1.13-1.66). After adjusting for antimycotic treatment and all confounders combined, onychomycosis remained significantly associated with ulcer development (HR 1.37, 95% CI 1.13-1.66 and HR 1.23, 95% CI 1.01 - 1.49, respectively).

Secondary outcomes

The results describing the association between onychomycosis and our secondary outcome measures, are also shown in Table 3.

Onychomycosis was significantly associated with hospital referrals in univariate analysis (HR 1.24, 95% CI 1.02-1.52). Adjusting for treatment did not significantly alter this association (HR 1.27, 95% CI 1.04-1.55). However, when adjusted for all confounders,

onychomycosis was not significantly associated with hospital referrals (HR 1.17, 95% CI 0.96-1.43).

Onychomycosis was also significantly associated with surgical interventions in primary care (HR 1.54, 95% CI 1.35-1.75). Antimycotic treatment did not significantly influence this association (HR 1.46, 95% CI 1.29-1.66), nor did adjustment for all confounders combined (HR 1.32, 95% CI 1.16-1.51).

Finally, onychomycosis was significantly associated with the bacterial infections cellulitis/erysipelas (HR 1.48, 95% CI 1.28-1.72), again not significantly affected by treatment (HR 1.45, 95% CI 1.25-1.68), nor after adjusting for all confounders (HR 1.27, 95% CI 1.10-1.48).

Table 3. Cox proportional-hazards models for effect of onychomycosis on primary and secondary outcome measures

Outcome	Onychomycosis		Univariate model		Adjusted for antimycotic treatment		Multivariate model *	
	Yes (%)	No (%)	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Primary								
Ulcer	140 (5.1)	2,631 (94.9)	1.37 (1.13 - 1.66)	0.001	1.37 (1.13 - 1.66)	0.001	1.23 (1.01-1.49)	0.036
Secondary								
Hospital referral	186 (6.1)	2874 (93.6)	1.24 (1.02-1.52)	0.035	1.27 (1.04-1.55)	0.021	1.17 (0.96-1.43)	0.128
Surgical intervention	427 (6.9)	5722 (93.1)	1.54 (1.35-1.75)	<0.001	1.46 (1.29-1.66)	<0.001	1.32 (1.16-1.51)	<0.001
Cellulitis / erysipelas	317 (6.5)	4572 (93.5)	1.48 (1.28-1.72)	<0.001	1.45 (1.25-1.68)	<0.001	1.27 (1.10-1.48)	0.001

* Adjusted for: age, sex, peripheral arterial disease, venous insufficiency, ankle edema, tinea Pedis, psoriasis, lichen planus, eczema, neuropathy, smoking, antimycotic treatment (any)

Conclusions

Summary

Our study demonstrated that onychomycosis in primary care diabetic patients, was significantly associated with the development of an ulcer compared to patients without onychomycosis. Even when adjusted for antimycotic treatment and additional confounders, onychomycosis remained independently associated with ulcer development. The same association was found for bacterial skin infections and surgical procedures in primary care.

Comparison with existing literature

Our results confirm the association between onychomycosis and ulcer development previously found in other populations, establishing its important role in diabetic patients, independently from already well-established risk factors like vascular disease, neuropathy and pre-existing skin disease [9,11,26].

Boyko et al. found an adjusted HR of 1.58 (95% CI 1.16-2.16) in their final multivariate model but used prospective data from veterans, predominantly male (98%) and of higher average age (62.4) attending internal medicine clinics i.e. a different setting [11]. Monteiro-Soares et al., in their endeavor to optimize the prediction model as proposed by Boyko, also found a significant association between onychomycosis and ulcer development using data from patients attending a tertiary podiatry clinic. However, they did not include the effect of time, thus limited to logistical regression analyses and unable to produce HR's to compare our results with [27].

Furthermore, we were able to confirm the association between onychomycosis and surgical interventions as well as bacterial skin infections in primary care, previously suspected but not sufficiently supported by clinical evidence [28,29].

Strengths and limitations

The major strength of this study was the ability to analyze data from a large cohort of primary care patients, our results therefore being representative for primary care settings in general. Although the association between onychomycosis and ulcer development has been described as mentioned above, this is the first study that establishes this association in primary care [11].

In addition, we specifically evaluated the effect of antimycotic treatment on the association between onychomycosis and diabetic complications, which was addressed in the systematic review of Monteiro et al., but not previously done [9-11]. Since onychomycosis increased the hazard for developing an ulcer, one might speculate antimycotic treatment would decrease this hazard. However, it did not, suggesting antimycotic treatment was not effective in preventing ulcers, or that antimycotic treatment merely represents a selection of patients with more severe disease burden, already more prone to ulcer development due to other contributing factors.

An important limitation due to the use of observational, routine-care data, was our inability to proof a causal relationship between onychomycosis and ulcer development. The finding that antimycotic treatment did not significantly affect the association between onychomycosis and ulcers, also suggests that onychomycosis is probably a marker rather than a direct cause of ulcer development.

Another limitation is the inherent level of uncertainty that comes with routine-care data. For example, coding is not always accurate and registration has improved over the last decades; effects based on data registered by GPs in the past might differ from data more recently registered. This could lead to over- or underreporting. Also, looking at the cumulative incidence of onychomycosis in our study sample, a lower number was found than reported by population based studies likely due to the fact not all patients consulted their GP [14]. However, it is unlikely that these data-registration limitations would be different for those with or without onychomycosis within our study population, therefore probably not affecting our results.

In parallel, specific groups of patients were likely to be checked more often by their GP, e.g. those having more severe disease. Their chance of being diagnosed with onychomycosis would be higher compared to healthier individuals, which potentially could have introduced confounding by indication and an overestimation of the association found. However, when correcting for all confounders, the independent and significant contribution of onychomycosis remained intact, pleading against a substantial effect from this form of confounding.

Finally, we only analyzed a pre-specified, available set of variables, not including important predictors of previous ulcers or amputations. Our results therefore only represent ulcer risk in those without prior ulcers or amputation.

Implications for practice and future perspectives

In conclusion, our study demonstrates that onychomycosis is independently associated with ulcer development in diabetic patients in primary care. As ulcers may precede lower extremity amputations and ultimately increase mortality, our findings support the clinical relevance of onychomycosis in diabetic patients, emphasizing the importance of recognizing fungal toenail infections in diabetes care [30-32]. Therefore, we would recommend all healthcare professionals involved in the care of diabetic patients within primary care, to systematically check for the presence of onychomycosis during routine care.

Investigating if treatment of onychomycosis could reduce the risk of diabetic ulcer development and related complications by a prospective study design, could be an important next scientific step.

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Association between onychomycosis and ulcerative complications in diabetic patients: a longitudinal cohort study in Dutch general practice

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Abstract

Introduction: Diabetic foot ulcers are feared complications of diabetes mellitus, requiring extensive treatment and hospital admissions, ultimately leading to amputation and increased mortality. Different factors contribute to the development of foot ulcers and related complications. Onychomycosis, being more prevalent in diabetics, could be an important risk factor for developing ulcers and related infections. However, the association between onychomycosis and diabetic complications has not been well studied in primary care.

Research Design and Methods: To determine the impact of onychomycosis on ulcer development and related complications in diabetic patients in primary care, a longitudinal cohort study was carried out using routine care data from the Extramural LUMC Academic Network (ELAN). Survival analyses were performed through Cox proportional hazards models with time-dependent covariates.

Results: Data from 48,212 patients with a mean age of 58 at diagnosis of DM, predominantly type 2 (87.8%), were analyzed over a median follow-up of 10.3 years. 5.7% of patients developed an ulcer. Onychomycosis significantly increased the risk of ulcer development (HR 1.37, 95% CI 1.13 - 1.66), not affected by antimycotic treatment, nor after adjusting for confounders (HR 1.23, 95% CI 1.01-1.49). The same was found for surgical interventions (HR 1.54, 95% CI 1.35-1.75) and skin infections (HR 1.48, CI 95% 1.28-1.72), again not affected by treatment and significant after adjusting for confounders (HR 1.32, 95% CI 1.16-1.51 and HR 1.27, 95% CI 1.10-1.48, respectively).

Conclusions: Onychomycosis significantly increased the risk of ulcer development in patients with DM in primary care, independently of other risk factors. In addition, onychomycosis increased the risk of surgeries and infectious complications. These results underscore the importance of giving sufficient attention to onychomycosis in primary care and corresponding guidelines. Early identification of onychomycosis during screening and routine care provides a good opportunity for timely recognition of increased ulcer risk.

Keywords: *Onychomycosis, Diabetes Mellitus, Diabetic Foot, Ulcer, Cox Proportional-Hazards*

Strengths and limitations

- First large retrospective cohort study investigating the association between onychomycosis and diabetic complications using primary care data
- This study establishes the significant and independent association between onychomycosis and ulcerative complications in primary care
- Inherent to the use of routine-care data, results may have been influenced by potential over- and underreporting.
- Due to the use of observational data, no causal relationship between onychomycosis and ulcerative complications could be established.

Introduction

According to the International Diabetes Federation, an estimated 537 million people worldwide suffer from diabetes mellitus (DM) (1). In 2019, 1.1 million diabetic patients were registered in Dutch primary care, about 7% of the adult population (2). Complications of DM are the cause of significant morbidity and medical costs (3). With the prevalence of DM projected to continue to rise, prevention and management of diabetic complications are becoming increasingly important (2).

One of the most feared complications of DM is the diabetic foot, which includes diabetic foot ulcers (4). Ulcers often require extensive treatment and hospitalization, and can ultimately lead to lower extremity amputation (5). To prevent ulcer development and its consequences, early recognition of patients at risk is essential (6).

Various risk factors for ulcer development have been identified. The most prominent are prior ulcer or amputation, neuropathy, foot deformity, focal pressure points, and peripheral arterial disease (7). Furthermore, male gender, signs of microangiopathy, including visual impairment, poor glycemic control (i.e. elevated HbA1c levels), insulin therapy, and onychomycosis were identified as additional significant risk factors (8, 9).

Regarding the latter, diabetic patients are more prone to fungal infections in general and onychomycosis in particular: up to one-third of diabetic patients are estimated to have onychomycosis compared to 4.3% in the general population (10, 11). Although onychomycosis is often considered a nuisance and unesthetic at most, numerous studies have shown onychomycosis to have a substantial negative effect on the quality of life and predispose patients to complications such as bacterial infections, especially in diabetic patients (12-14). However, the underlying pathophysiologic mechanism that explains the relationship between onychomycosis and diabetic complications remains unclear (15, 16). Although previous studies suggest onychomycosis may be an important risk factor for ulcer development, this relationship has not been well studied in primary care (7, 17).

The aim of this study was to assess if onychomycosis, treated or not, is a risk factor for diabetic foot ulcers, and secondly, for related complications in primary care. Therefore, we conducted a longitudinal cohort study using routine-care data of diabetic patients from primary care.

Methods

Study design

This study was designed as a longitudinal, retrospective cohort using routine-care data from primary care patients with DM. The date of diagnosis of DM was considered the start of follow-up; the end of follow-up was either development of an outcome, date of death, deregistration or data extraction. Using pre-defined risk factors, primarily onychomycosis and secondarily antimycotic treatment and related, often underlying conditions, both exposed and unexposed individuals were identified. Following patients forward in time, the incidences of the outcomes of interest were compared between the two groups (18). Ulcer development was considered the primary outcome; hospital referrals, surgical interventions (performed within primary care), and the bacterial skin infections cellulitis and erysipelas, were secondary outcomes.

Data and setting

Routine-care data from primary care practices affiliated with the Extramural LUMC (Leiden University Medical Center) Academic Network (ELAN) were used. ELAN is a collaboration between Dutch general practitioners and the Department of Public Health and Primary Care (PHEG) from the LUMC, in the western part of the Netherlands. ELAN periodically extracts and stores these data in their database in compliance with local and European privacy legislation (19, 20). The investigators had no access to the ELAN database used to create the dataset for analysis. The data used to create the dataset provided to the investigators, were extracted on May 11th, 2022.

Participants

The records of all diabetic patients, regardless of subtype, were extracted. Based on the intended analyses, patient records meeting the following criteria were selected:

1. Date of diagnosis of DM recorded
2. Age between 0-100
3. Date of exposure (risk factor) and event (complication) recorded, i.e. time between diagnosis of DM and exposure or outcome of interest known

4. Exposure or event occurred after diagnosis of DM and before deregistration, death or data extraction, i.e. during follow-up

Regarding the latter, since the start of follow-up was defined as the date on which the diagnosis of DM was established, only exposures and events occurring after baseline were used for analyses.

Patient and Public Involvement

It was not appropriate to involve patients or the public in the design, conduct, reporting, or dissemination plans of our research.

Measurements and Outcomes

Regarding exposures and outcome measures, the diagnoses and comorbidities extracted were coded using the International Classification of Primary Care (ICPC) coding system and their corresponding dates of registration. Similarly, data on medication, referrals, and interventions were extracted using their corresponding coding systems.

Besides onychomycosis, the available risk factors of interest were tinea pedis, peripheral artery disease, venous insufficiency, ankle edema, psoriasis, lichen planus, eczema, neuropathy, smoking, and antimycotic treatment. In addition, age and sex were also considered potential confounders and used for analyses.

Our primary outcome measure was ulcer development. Secondary outcome measures were hospital referrals, surgical interventions performed within primary care, i.e. minor procedures such as debridement, and infectious complications (cellulitis and erysipelas). Only hospital referrals related to DM referring to surgery, internal medicine or dermatology, were used for analyses.

Cellulitis and erysipelas, although coded differently, were combined since both entities are used interchangeably. The same was done for ulcus cruris and diabetic foot ulcers, combining them into a single variable for ulcers. In case two variables were combined and a patient was diagnosed with having both, the diagnosis that occurred first, i.e. with the shortest time to diagnosis of DM, was used for analysis.

Statistical analyses

Descriptive statistics were used to analyze patient characteristics at baseline and to describe the occurrence of both exposures and outcomes during follow-up.

Since exposures and outcomes of interest were not constant over time, i.e. occurring at different moments during follow-up, these were considered to be time-dependent covariates. Therefore, to answer our research questions, Cox-proportional hazards models with time-dependent covariates were used, thus taking into account the time between baseline and diagnosis of an exposure or event. The proportional hazard (PH) assumption was checked by testing whether the covariates interacted significantly with time. In case of violation, the corresponding hazard ratio (HR) was modelled as a time-dependent effect by including an interaction term between the logarithm of time and the covariate.

To answer our research questions, three models were constructed. First, the association between onychomycosis and ulcer development was evaluated as single predictor (univariate model), then adjusted for antimycotic treatment (first multivariate model), and finally for all potential confounders mentioned above (second multivariate model). The proportional hazards assumption (PH) was violated for age and neuropathy in the last model, hence corrected for by including the interaction terms with the logarithm of time in the corresponding model.

Regarding secondary outcomes, the associations between onychomycosis and hospital referrals, surgeries, and bacterial skin infections were evaluated. The same set of models, i.e. a univariate model, a multivariate model to adjust for antimycotic treatment and a final multivariate model to adjust for all confounders combined, were used for each of the secondary outcomes, respectively. Again, the interaction terms with the logarithm of time were used for the covariates for which the PH-assumption was violated. These were neuropathy and smoking in the final multivariate model for hospital referrals, age and ankle edema in the final model for surgical interventions, and age in the final model for bacterial skin infections.

P-values of <0.05 were considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics (Version 28).

Results

Patient characteristics

The initial data extraction consisted of 50,292 patient records. After applying the criteria as described, 48,212 records were selected for analysis. Patient characteristics are shown in Table 1. Our sample included 22,877 women (47.5%) and 25,335 men (52.5%). The mean age at baseline was 58.3 years (SD 15.7). The vast majority of patients (87.8%) were diagnosed with type 2 DM; only 6.5% had type 1 DM and the remaining cases (5.7%) were unspecified.

Table 1. Patient characteristics	
Patients, total (N)	48,212
Mean age at onset of DM in years (SD)	58.3 (15.7)
Gender, N (%)	
Male	25,335 (52.5)
Female	22,877 (47.5)
Type of Diabetes Mellitus, N (%)	
Type 1	3,131 (6.5)
Type 2	42,312 (87.8)
Unspecified	2,769 (5.7)

Table 1. Patient characteristics at baseline i.e. start of follow-up.

The median follow-up time was 10.3 years (IQR 10.8). Exposures and events recorded during follow-up are presented in Table 2.

The cumulative incidence of onychomycosis in our sample was 4.1%. Regarding the other exposures, ankle edema (13.5%) and eczema (12.2%) were most frequently recorded. During follow-up, 6.2% of patients received any form of antimycotic treatment. In total 2,771 patients (5.7%) developed an ulcer after a median of 8.8 years (IQR 9.6). Regarding the secondary outcomes, surgical interventions occurred most frequently (12.8%) after a median of 7.8 years (IQR 8.9), followed by infections (10.1%) after a median 7.7 years (IQR 9.4). 6.3% needed a hospital referral after a median of 7.4 years (IQR 9.2).

Table 2. Exposures and events during follow-up	
	N (cumulative incidence, %)
Total cohort	48,212
Exposures	
Onychomycosis	1,959 (4.1)
Tinea pedis	2,006 (4.2)
Peripheral arterial disease	2,381 (4.9)
Venous insufficiency	275 (0.6)
Ankle edema	6,494 (13.5)
Psoriasis	1,193 (2.5)
Lichen ruber planus	166 (0.3)
Eczema	5,870 (12.2)
Neuropathy	3,287 (6.8)
Smoking	2,930 (6.1)
Antimycotic treatment	
Any type	3,005 (6.2)
Local	2,777 (5.8)
Systemic	228 (0.5)
Events	
Ulcer	2,771 (5.7)
Cellulitis/erysipelas	4,889 (10.1)
Hospital referral	3,060 (6.3)
Surgical intervention	6,149 (12.8)

Table 2. Overview of exposures and events during follow-up.

Primary outcome: ulcer development

The results for the association between onychomycosis and ulcer development are shown in Table 3. In univariate analysis, onychomycosis was significantly associated with ulcer development (HR 1.37, 95% CI 1.13-1.66). After adjusting for antimycotic treatment and all confounders combined, onychomycosis remained significantly associated with ulcer development (HR 1.37, 95% CI 1.13-1.66 and HR 1.23, 95% CI 1.01 - 1.49, respectively).

Secondary outcomes

The results describing the association between onychomycosis and our secondary outcome measures, are also shown in Table 3.

Onychomycosis was significantly associated with hospital referrals in univariate analysis (HR 1.24, 95% CI 1.02-1.52). Adjusting for treatment did not significantly alter this association (HR 1.27, 95% CI 1.04-1.55). However, when adjusted for all confounders,

onychomycosis was not significantly associated with hospital referrals (HR 1.17, 95% CI 0.96-1.43).

Onychomycosis was also significantly associated with surgical interventions in primary care (HR 1.54, 95% CI 1.35-1.75). Antimycotic treatment did not significantly influence this association (HR 1.46, 95% CI 1.29-1.66), nor did adjustment for all confounders combined (HR 1.32, 95% CI 1.16-1.51).

Finally, onychomycosis was significantly associated with the bacterial infections cellulitis/erysipelas (HR 1.48, 95% CI 1.28-1.72), again not significantly affected by treatment (HR 1.45, 95% CI 1.25-1.68), nor after adjusting for all confounders (HR 1.27, 95% CI 1.10-1.48).

Table 3. Cox proportional-hazards models for effect of onychomycosis on primary and secondary outcome measures

Outcome	Onychomycosis		Univariate model		Adjusted for antimycotic treatment		Multivariate model *	
	Yes (%)	No (%)	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Primary								
Ulcer	140 (5.1)	2,631 (94.9)	1.37 (1.13 - 1.66)	0.001	1.37 (1.13 - 1.66)	0.001	1.23 (1.01-1.49)	0.036
Secondary								
Hospital referral	186 (6.1)	2874 (93.6)	1.24 (1.02-1.52)	0.035	1.27 (1.04-1.55)	0.021	1.17 (0.96-1.43)	0.128
Surgical intervention	427 (6.9)	5722 (93.1)	1.54 (1.35-1.75)	<0.001	1.46 (1.29-1.66)	<0.001	1.32 (1.16-1.51)	<0.001
Cellulitis / erysipelas	317 (6.5)	4572 (93.5)	1.48 (1.28-1.72)	<0.001	1.45 (1.25-1.68)	<0.001	1.27 (1.10-1.48)	0.001

* Adjusted for: age, sex, peripheral arterial disease, venous insufficiency, ankle edema, tinea pedis, psoriasis, lichen planus, eczema, neuropathy, smoking, antimycotic treatment (any)

Conclusions

Summary

Our study demonstrated that onychomycosis in primary care diabetic patients, was significantly associated with the development of an ulcer compared to patients without onychomycosis. Even when adjusted for antimycotic treatment and additional confounders, onychomycosis remained independently associated with ulcer development. The same association was found for bacterial skin infections and surgical procedures in primary care.

Comparison with existing literature

Our results confirm the association between onychomycosis and ulcer development previously found in other populations, establishing its important role in diabetic patients, independently from already well-established risk factors like vascular disease, neuropathy and pre-existing skin disease (7, 8, 21).

Boyko et al. found an adjusted HR of 1.58 (95% CI 1.16-2.16) in their final multivariate model but used prospective data from veterans, predominantly male (98%) and of higher average age (62.4) attending internal medicine clinics i.e. a different setting (8). Monteiro-Soares et al., in their endeavor to optimize the prediction model as proposed by Boyko, also found a significant association between onychomycosis and ulcer development using data from patients attending a tertiary podiatry clinic. However, they did not include the effect of time, thus limited to logistical regression analyses and unable to produce HR's to compare our results with (22).

Furthermore, we were able to confirm the association between onychomycosis and surgical interventions as well as bacterial skin infections in primary care, previously suspected but not sufficiently supported by clinical evidence (23, 24).

Strengths and limitations

The major strength of this study was the ability to analyze data from a large cohort of primary care patients, our results therefore being representative for primary care settings in general. Although the association between onychomycosis and ulcer development has been described as mentioned above, this is the first study that establishes this association in primary care (8).

In addition, we specifically evaluated the effect of antimycotic treatment on the association between onychomycosis and diabetic complications, which was addressed in the systematic review of Monteiro et al., but not previously done (7, 8, 25). Since onychomycosis increased the hazard for developing an ulcer, one might speculate antimycotic treatment would decrease this hazard. However, it did not, suggesting antimycotic treatment was not effective in preventing ulcers, or that antimycotic treatment merely represents a selection of patients with more severe disease burden, already more prone to ulcer development due to other contributing factors.

An important limitation due to the use of observational, routine-care data, was our inability to proof a causal relationship between onychomycosis and ulcer development. The finding that antimycotic treatment did not significantly affect the association between onychomycosis and ulcers, also suggests that onychomycosis is probably a marker rather than a direct cause of ulcer development.

Another limitation is the inherent level of uncertainty that comes with routine-care data. For example, coding is not always accurate and registration has improved over the last decades; effects based on data registered by GPs in the past might differ from data more recently registered. This could lead to over- or underreporting. Also, looking at the cumulative incidence of onychomycosis in our study sample, a lower number was found than reported by population based studies likely due to the fact not all patients consulted their GP (10). However, it is unlikely that these data-registration limitations would be different for those with or without onychomycosis within our study population, therefore probably not affecting our results.

In parallel, specific groups of patients were likely to be checked more often by their GP, e.g. those having more severe disease. Their chance of being diagnosed with onychomycosis would be higher compared to healthier individuals, which potentially could have introduced confounding by indication and an overestimation of the association found. However, when correcting for all confounders, the independent and significant contribution of onychomycosis remained intact, pleading against a substantial effect from this form of confounding.

Finally, we only analyzed a pre-specified, available set of variables, not including important predictors of previous ulcers or amputations. Our results therefore only represent ulcer risk in those without prior ulcers or amputation.

Implications for practice and future perspectives

In conclusion, our study demonstrates that onychomycosis is independently associated with ulcer development in diabetic patients in primary care. As ulcers may precede lower extremity amputations and ultimately increase mortality, our findings support the clinical relevance of onychomycosis in diabetic patients, emphasizing the importance of recognizing fungal toenail infections in diabetes care (26-28). Therefore, we would recommend all healthcare professionals involved in the care of diabetic patients within primary care, to systematically check for the presence of onychomycosis during routine care.

Investigating if treatment of onychomycosis could reduce the risk of diabetic ulcer development and related complications by a prospective study design, could be an important next scientific step.

Contributorship statement

All authors read and approved the final manuscript. RW, JE, and TB: conceptualization; RW, KH, LG, and TB: methodology and formal analysis; RW, KH, and LG: investigation, data curation, writing; RW, JE, KQ, ME, and TB: review; TN and JE: supervision.

Competing interests

The authors declare that they have no competing interests.

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Data sharing statement

Data are available upon reasonable request.

Ethics approval statement

Medical Ethics Committee Leiden Den-Haag Delft (METC-LDD), reference number G21.206. The METC-LDD decided that, in accordance with national regulations, further approval by an institutional review board was not necessary i.e. a waiver was granted and the study was exempted since the study was not subject to the Medical Research Involving Human Subjects Act, according to the guidelines of the Central Committee on Research Involving Human Subjects (CCMO). For additional information in English, please refer to: https://english.ccmo.nl/investigators/legal-framework-for-medical-scientific-research/your-research-is-it-subject-to-the-wmo-or-not or in Dutch: https://wetten.overheid.nl/jci1.3:c:BWBR0009408&z=2022-03-15&g=2022-03-15.

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was f	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow, and data collection	5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5,6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	n.a.
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5
Bias	9	Describe any efforts to address potential sources of bias	5,6
Study size	10	Explain how the study size was arrived at	5,6

Continued on next page

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	n.a.
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	n.a.
		(*e*) Describe any sensitivity analyses	n.a.
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	n.a.
		(c) Consider use of a flow diagram	n.a.
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8
		(b) Indicate number of participants with missing data for each variable of interest	n.a.
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	8
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	9
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	n.a.
		Cross-sectional study—Report numbers of outcome events or summary measures	n..a
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9,10
		(*b*) Report category boundaries when continuous variables were categorized	n.a.
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n.a.

Continued on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	n.a.
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11,12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13
Generalisability	21	Discuss the generalisability (external validity) of the study results	12,13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	n.a.

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Association between onychomycosis and ulcerative complications in patients with diabetes: a longitudinal cohort study in Dutch general practice

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Abstract

Introduction: Diabetic foot ulcers are feared complications of diabetes mellitus, requiring extensive treatment and hospital admissions, ultimately leading to amputation and increased mortality. Different factors contribute to the development of foot ulcers and related complications. Onychomycosis, being more prevalent in patients with diabetes, could be an important risk factor for developing ulcers and related infections. However, the association between onychomycosis and diabetic complications has not been well studied in primary care.

Research Design and Methods: To determine the impact of onychomycosis on ulcer development and related complications in patients with diabetes in primary care, a longitudinal cohort study was carried out using routine care data from the Extramural LUMC Academic Network (ELAN). Survival analyses were performed through Cox proportional hazards models with time-dependent covariates.

Results: Data from 48,212 patients with a mean age of 58 at diagnosis of DM, predominantly type 2 (87.8%), were analyzed over a median follow-up of 10.3 years. 5.7% of patients developed an ulcer. Onychomycosis significantly increased the risk of ulcer development (HR 1.37, 95% CI 1.13 - 1.66), not affected by antimycotic treatment, nor after adjusting for confounders (HR 1.23, 95% CI 1.01-1.49). The same was found for surgical interventions (HR 1.54, 95% CI 1.35-1.75) and skin infections (HR 1.48, CI 95% 1.28-1.72), again not affected by treatment and significant after adjusting for confounders (HR 1.32, 95% CI 1.16-1.51 and HR 1.27, 95% CI 1.10-1.48, respectively).

Conclusions: Onychomycosis significantly increased the risk of ulcer development in patients with DM in primary care, independently of other risk factors. In addition, onychomycosis increased the risk of surgeries and infectious complications. These results underscore the importance of giving sufficient attention to onychomycosis in primary care and corresponding guidelines. Early identification of onychomycosis during screening and routine care provides a good opportunity for timely recognition of increased ulcer risk.

Keywords: *Onychomycosis, Diabetes Mellitus, Diabetic Foot, Ulcer, Cox Proportional-Hazards*

Strengths and limitations

- First large retrospective cohort study investigating the association between onychomycosis and diabetic complications using primary care data
- This study establishes the significant and independent association between onychomycosis and ulcerative complications in primary care
- Inherent to the use of routine-care data, results may have been influenced by potential over- and underreporting.
- Due to the use of observational data, no causal relationship between onychomycosis and ulcerative complications could be established.

Introduction

According to the International Diabetes Federation, an estimated 537 million people worldwide suffer from diabetes mellitus (DM) (1). In 2019, 1.1 million patients with diabetes were registered in Dutch primary care, about 7% of the adult population (2). Complications of DM are the cause of significant morbidity and medical costs (3). With the prevalence of DM projected to continue to rise, prevention and management of diabetic complications are becoming increasingly important (2).

One of the most feared complications of DM is the diabetic foot, which includes diabetic foot ulcers (4). Ulcers often require extensive treatment and hospitalization, and can ultimately lead to lower extremity amputation (5). To prevent ulcer development and its consequences, early recognition of patients at risk is essential (6).

Various risk factors for ulcer development have been identified. The most prominent are prior ulcer or amputation, neuropathy, foot deformity, focal pressure points, and peripheral arterial disease (7). Furthermore, male gender, signs of microangiopathy, including visual impairment, poor glycemic control (i.e. elevated HbA1c levels), insulin therapy, and onychomycosis were identified as additional significant risk factors (8, 9).

Regarding the latter, patients with diabetes are more prone to fungal infections in general and onychomycosis in particular: up to one-third of patients with diabetes are estimated to have onychomycosis compared to 4.3% in the general population (10, 11). Although onychomycosis is often considered a nuisance and unesthetic at most, numerous studies have shown onychomycosis to have a substantial negative effect on the quality of life and predispose patients to complications such as bacterial infections, especially in patients with diabetes (12-14). However, the underlying pathophysiologic mechanism that explains the relationship between onychomycosis and diabetic complications remains unclear (15, 16). Although previous studies suggest onychomycosis may be an important risk factor for ulcer development, this relationship has not been well studied in primary care (7, 17).

The aim of this study was to assess if onychomycosis, treated or not, is a risk factor for diabetic foot ulcers, and secondly, for related complications in primary care. Therefore, we conducted a longitudinal cohort study using routine-care data of patients with diabetes from primary care.

Methods

Study design

This study was designed as a longitudinal, retrospective cohort using routine-care data from primary care patients with DM. The date of diagnosis of DM was considered the start of follow-up; the end of follow-up was either development of an outcome, date of death, deregistration or data extraction. Using pre-defined risk factors, primarily onychomycosis and secondarily antimycotic treatment and related, often underlying conditions, both exposed and unexposed individuals were identified. Following patients forward in time, the incidences of the outcomes of interest were compared between the two groups (18). Ulcer development was considered the primary outcome; hospital referrals, surgical interventions (performed within primary care), and the bacterial skin infections cellulitis and erysipelas, were secondary outcomes.

Data and setting

Routine-care data from primary care practices affiliated with the Extramural LUMC (Leiden University Medical Center) Academic Network (ELAN) were used. ELAN is a collaboration between Dutch general practitioners and the Department of Public Health and Primary Care (PHEG) from the LUMC, in the western part of the Netherlands. ELAN periodically extracts and stores these data in their database in compliance with local and European privacy legislation (19, 20). The investigators had no access to the ELAN database used to create the dataset for analysis. The data used to create the dataset provided to the investigators, were extracted on May 11th, 2022.

Participants

The records of all patients with diabetes, regardless of subtype, were extracted. Based on the intended analyses, patient records meeting the following criteria were selected:

1. Date of diagnosis of DM recorded
2. Age between 0-100
3. Date of exposure (risk factor) and event (complication) recorded, i.e. time between diagnosis of DM and exposure or outcome of interest known

4. Exposure or event occurred after diagnosis of DM and before deregistration, death or data extraction, i.e. during follow-up

Regarding the latter, since the start of follow-up was defined as the date on which the diagnosis of DM was established, only exposures and events occurring after baseline were used for analyses.

Patient and Public Involvement

It was not appropriate to involve patients or the public in the design, conduct, reporting, or dissemination plans of our research.

Measurements and Outcomes

Regarding exposures and outcome measures, the diagnoses and comorbidities extracted were coded using the International Classification of Primary Care (ICPC) coding system and their corresponding dates of registration. Similarly, data on medication, referrals, and interventions were extracted using their corresponding coding systems.

Besides onychomycosis, the available risk factors of interest were tinea pedis, peripheral artery disease, venous insufficiency, ankle edema, psoriasis, lichen planus, eczema, neuropathy, smoking, and antimycotic treatment. In addition, age and sex were also considered potential confounders and used for analyses.

Our primary outcome measure was ulcer development. Secondary outcome measures were hospital referrals, surgical interventions performed within primary care, i.e. minor procedures such as debridement, and infectious complications (cellulitis and erysipelas). Only hospital referrals related to DM referring to surgery, internal medicine or dermatology, were used for analyses.

Cellulitis and erysipelas, although coded differently, were combined since both entities are used interchangeably. The same was done for ulcus cruris and diabetic foot ulcers, combining them into a single variable for ulcers. In case two variables were combined and a patient was diagnosed with having both, the diagnosis that occurred first, i.e. with the shortest time to diagnosis of DM, was used for analysis.

Statistical analyses

Descriptive statistics were used to analyze patient characteristics at baseline and to describe the occurrence of both exposures and outcomes during follow-up.

Since exposures and outcomes of interest were not constant over time, i.e. occurring at different moments during follow-up, these were considered to be time-dependent covariates. Therefore, to answer our research questions, Cox-proportional hazards models with time-dependent covariates were used, thus taking into account the time between baseline and diagnosis of an exposure or event. The proportional hazard (PH) assumption was checked by testing whether the covariates interacted significantly with time. In case of violation, the corresponding hazard ratio (HR) was modelled as a time-dependent effect by including an interaction term between the logarithm of time and the covariate.

To answer our research questions, three models were constructed. First, the association between onychomycosis and ulcer development was evaluated as single predictor (univariate model), then adjusted for antimycotic treatment (first multivariate model), and finally for all potential confounders mentioned above (second multivariate model). The proportional hazards assumption (PH) was violated for age and neuropathy in the last model, hence corrected for by including the interaction terms with the logarithm of time in the corresponding model.

Regarding secondary outcomes, the associations between onychomycosis and hospital referrals, surgeries, and bacterial skin infections were evaluated. The same set of models, i.e. a univariate model, a multivariate model to adjust for antimycotic treatment and a final multivariate model to adjust for all confounders combined, were used for each of the secondary outcomes, respectively. Again, the interaction terms with the logarithm of time were used for the covariates for which the PH-assumption was violated. These were neuropathy and smoking in the final multivariate model for hospital referrals, age and ankle edema in the final model for surgical interventions, and age in the final model for bacterial skin infections.

P-values of <0.05 were considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics (Version 28).

Results

Patient characteristics

The initial data extraction consisted of 50,292 patient records. After applying the criteria as described, 48,212 records were selected for analysis. Patient characteristics are shown in Table 1. Our sample included 22,877 women (47.5%) and 25,335 men (52.5%). The mean age at baseline was 58.3 years (SD 15.7). The vast majority of patients (87.8%) were diagnosed with type 2 DM; only 6.5% had type 1 DM and the remaining cases (5.7%) were unspecified.

Table 1. Patient characteristics	
Patients, total (N)	48,212
Mean age at onset of DM in years (SD)	58.3 (15.7)
Gender, N (%)	
Male	25,335 (52.5)
Female	22,877 (47.5)
Type of Diabetes Mellitus, N (%)	
Type 1	3,131 (6.5)
Type 2	42,312 (87.8)
Unspecified	2,769 (5.7)

Table 1. Patient characteristics at baseline i.e. start of follow-up.

The median follow-up time was 10.3 years (IQR 10.8). Exposures and events recorded during follow-up are presented in Table 2.

The cumulative incidence of onychomycosis in our sample was 4.1%. Regarding the other exposures, ankle edema (13.5%) and eczema (12.2%) were most frequently recorded. During follow-up, 6.2% of patients received any form of antimycotic treatment. In total 2,771 patients (5.7%) developed an ulcer after a median of 8.8 years (IQR 9.6). Regarding the secondary outcomes, surgical interventions occurred most frequently (12.8%) after a median of 7.8 years (IQR 8.9), followed by infections (10.1%) after a median 7.7 years (IQR 9.4). 6.3% needed a hospital referral after a median of 7.4 years (IQR 9.2).

Table 2. Exposures and events during follow-up	
	N (cumulative incidence, %)
Total cohort	48,212
Exposures	
Onychomycosis	1,959 (4.1)
Tinea pedis	2,006 (4.2)
Peripheral arterial disease	2,381 (4.9)
Venous insufficiency	275 (0.6)
Ankle edema	6,494 (13.5)
Psoriasis	1,193 (2.5)
Lichen ruber planus	166 (0.3)
Eczema	5,870 (12.2)
Neuropathy	3,287 (6.8)
Smoking	2,930 (6.1)
Antimycotic treatment	
Any type	3,005 (6.2)
Local	2,777 (5.8)
Systemic	228 (0.5)
Events	
Ulcer	2,771 (5.7)
Cellulitis/erysipelas	4,889 (10.1)
Hospital referral	3,060 (6.3)
Surgical intervention	6,149 (12.8)

Table 2. Overview of exposures and events during follow-up.

Primary outcome: ulcer development

The results for the association between onychomycosis and ulcer development are shown in Table 3. In univariate analysis, onychomycosis was significantly associated with ulcer development (HR 1.37, 95% CI 1.13-1.66). After adjusting for antimycotic treatment and all confounders combined, onychomycosis remained significantly associated with ulcer development (HR 1.37, 95% CI 1.13-1.66 and HR 1.23, 95% CI 1.01 - 1.49, respectively).

Secondary outcomes

The results describing the association between onychomycosis and our secondary outcome measures, are also shown in Table 3.

Onychomycosis was significantly associated with hospital referrals in univariate analysis (HR 1.24, 95% CI 1.02-1.52). Adjusting for treatment did not significantly alter this association (HR 1.27, 95% CI 1.04-1.55). However, when adjusted for all confounders,

onychomycosis was not significantly associated with hospital referrals (HR 1.17, 95% CI 0.96-1.43).

Onychomycosis was also significantly associated with surgical interventions in primary care (HR 1.54, 95% CI 1.35-1.75). Antimycotic treatment did not significantly influence this association (HR 1.46, 95% CI 1.29-1.66), nor did adjustment for all confounders combined (HR 1.32, 95% CI 1.16-1.51).

Finally, onychomycosis was significantly associated with the bacterial infections cellulitis/erysipelas (HR 1.48, 95% CI 1.28-1.72), again not significantly affected by treatment (HR 1.45, 95% CI 1.25-1.68), nor after adjusting for all confounders (HR 1.27, 95% CI 1.10-1.48).

Table 3. Cox proportional-hazards models for effect of onychomycosis on primary and secondary outcome measures

Outcome	Onychomycosis		Univariate model		Adjusted for antimycotic treatment		Multivariate model *	
	Yes (%)	No (%)	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Primary								
Ulcer	140 (5.1)	2,631 (94.9)	1.37 (1.13 - 1.66)	0.001	1.37 (1.13 - 1.66)	0.001	1.23 (1.01-1.49)	0.036
Secondary								
Hospital referral	186 (6.1)	2874 (93.6)	1.24 (1.02-1.52)	0.035	1.27 (1.04-1.55)	0.021	1.17 (0.96-1.43)	0.128
Surgical intervention	427 (6.9)	5722 (93.1)	1.54 (1.35-1.75)	<0.001	1.46 (1.29-1.66)	<0.001	1.32 (1.16-1.51)	<0.001
Cellulitis / erysipelas	317 (6.5)	4572 (93.5)	1.48 (1.28-1.72)	<0.001	1.45 (1.25-1.68)	<0.001	1.27 (1.10-1.48)	0.001

* Adjusted for: age, sex, peripheral arterial disease, venous insufficiency, ankle edema, tinea pedis, psoriasis, lichen planus, eczema, neuropathy, smoking, antimycotic treatment (any)

Conclusions

Summary

Our study demonstrated that onychomycosis in primary care patients with diabetes, was significantly associated with the development of an ulcer compared to patients without onychomycosis. Even when adjusted for antimycotic treatment and additional confounders, onychomycosis remained independently associated with ulcer development. The same association was found for bacterial skin infections and surgical procedures in primary care.

Comparison with existing literature

Our results confirm the association between onychomycosis and ulcer development previously found in other populations, establishing its important role in patients with diabetes, independently from already well-established risk factors like vascular disease, neuropathy and pre-existing skin disease (7, 8, 21).

Boyko et al. found an adjusted HR of 1.58 (95% CI 1.16-2.16) in their final multivariate model but used prospective data from veterans, predominantly male (98%) and of higher average age (62.4) attending internal medicine clinics i.e. a different setting (8). Monteiro-Soares et al., in their endeavor to optimize the prediction model as proposed by Boyko, also found a significant association between onychomycosis and ulcer development using data from patients attending a tertiary podiatry clinic. However, they did not include the effect of time, thus limited to logistical regression analyses and unable to produce HR's to compare our results with (22).

Furthermore, we were able to confirm the association between onychomycosis and surgical interventions as well as bacterial skin infections in primary care, previously suspected but not sufficiently supported by clinical evidence (23, 24).

Strengths and limitations

The major strength of this study was the ability to analyze data from a large cohort of primary care patients, our results therefore being representative for primary care settings in general. Although the association between onychomycosis and ulcer development has been described as mentioned above, this is the first study that establishes this association in primary care (8).

In addition, we specifically evaluated the effect of antimycotic treatment on the association between onychomycosis and diabetic complications, which was addressed in the systematic review of Monteiro et al., but not previously done (7, 8, 25). Since onychomycosis increased the hazard for developing an ulcer, one might speculate antimycotic treatment would decrease this hazard. However, it did not, suggesting antimycotic treatment was not effective in preventing ulcers, or that antimycotic treatment merely represents a selection of patients with more severe disease burden, already more prone to ulcer development due to other contributing factors.

An important limitation due to the use of observational, routine-care data, was our inability to proof a causal relationship between onychomycosis and ulcer development. The finding that antimycotic treatment did not significantly affect the association between onychomycosis and ulcers, also suggests that onychomycosis is probably a marker rather than a direct cause of ulcer development.

Another limitation is the inherent level of uncertainty that comes with routine-care data. For example, coding is not always accurate and registration has improved over the last decades; effects based on data registered by GPs in the past might differ from data more recently registered. This could lead to over- or underreporting. Also, looking at the cumulative incidence of onychomycosis in our study sample, a lower number was found than reported by population based studies likely due to the fact not all patients consulted their GP (10). However, it is unlikely that these data-registration limitations would be different for those with or without onychomycosis within our study population, therefore probably not affecting our results.

In parallel, specific groups of patients were likely to be checked more often by their GP, e.g. those having more severe disease. Their chance of being diagnosed with onychomycosis would be higher compared to healthier individuals, which potentially could have introduced confounding by indication and an overestimation of the association found. However, when correcting for all confounders, the independent and significant contribution of onychomycosis remained intact, pleading against a substantial effect from this form of confounding.

Finally, we only analyzed a pre-specified, available set of variables, not including important predictors of previous ulcers or amputations. Our results therefore only represent ulcer risk in those without prior ulcers or amputation.

Implications for practice and future perspectives

In conclusion, our study demonstrates that onychomycosis is independently associated with ulcer development in patients with diabetes in primary care. As ulcers may precede lower extremity amputations and ultimately increase mortality, our findings support the clinical relevance of onychomycosis in patients with diabetes, emphasizing the importance of recognizing fungal toenail infections in diabetes care (26-28). Therefore, we would recommend all healthcare professionals involved in the care of patients with diabetes within primary care, to systematically check for the presence of onychomycosis during routine care.

Investigating if treatment of onychomycosis could reduce the risk of diabetic ulcer development and related complications by a prospective study design, could be an important next scientific step.

Contributorship statement

All authors read and approved the final manuscript. RW, JE, and TB: conceptualization; RW, KH, LG, and TB: methodology and formal analysis; RW, KH, and LG: investigation, data curation, writing; RW, JE, KQ, MN, and TB: review; TN and JE: supervision.

Competing interests

The authors declare that they have no competing interests.

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Data sharing statement

Data are available upon reasonable request.

Ethics approval statement

Medical Ethics Committee Leiden Den-Haag Delft (METC-LDD), reference number G21.206. The METC-LDD decided that, in accordance with national regulations, further approval by an institutional review board was not necessary i.e. a waiver was granted and the study was exempted since the study was not subject to the Medical Research Involving Human Subjects Act, according to the guidelines of the Central Committee on Research Involving Human Subjects (CCMO). For additional information in English, please refer to: https://english.ccmo.nl/investigators/legal-framework-for-medical-scientific-research/your-research-is-it-subject-to-the-wmo-or-not or in Dutch: https://wetten.overheid.nl/jci1.3:c:BWBR0009408&z=2022-03-15&g=2022-03-15.

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was f	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow, and data collection	5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5,6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	n.a.
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5
Bias	9	Describe any efforts to address potential sources of bias	5,6
Study size	10	Explain how the study size was arrived at	5,6

Continued on next page

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	n.a.
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	n.a.
		(*e*) Describe any sensitivity analyses	n.a.
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	n.a.
		(c) Consider use of a flow diagram	n.a.
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8
		(b) Indicate number of participants with missing data for each variable of interest	n.a.
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	8
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	9
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	n.a.
		Cross-sectional study—Report numbers of outcome events or summary measures	n..a
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9,10
		(*b*) Report category boundaries when continuous variables were categorized	n.a.
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n.a.

Continued on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	n.a.
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11,12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13
Generalisability	21	Discuss the generalisability (external validity) of the study results	12,13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	n.a.

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.