

PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Association between onychomycosis and ulcerative complications in patients with diabetes: a longitudinal cohort study in Dutch general practice
AUTHORS	Watjer, Roeland; Heckmans, Kim; Eekhof, Just; Gummi, Luise; Quint, Koen D.; Numans, Mattijs; Bonten, Tobias N.

VERSION 1 – REVIEW

REVIEWER	Tapia, María Gabriela Morgado Universidad Andres Bello, Nursing Faculty
REVIEW RETURNED	19-Jun-2023

GENERAL COMMENTS	<p>1. The study doesn't declare how it accessed the data and how its confidentiality was protected, under local regulations.</p> <p>2. It's necessary to update references. Most of them are over 10 years old.</p> <p>3. It is recommended to review the description of statistical analysis.</p>
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REVIEWER	Ekeng, Bassey E. Medical Mycology Society of Nigeria
REVIEW RETURNED	03-Jul-2023

GENERAL COMMENTS	<p>This is a great work. However do upgrade the section on introduction.</p> <p>The study design seems retrospective. Kindly ratify as per the appended comments</p> <p>(The reviewer provided a marked copy with additional comments. Please contact the publisher for full details.)</p>
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REVIEWER	Gamba, Monica Antar Universidade Federal de São Paulo
REVIEW RETURNED	05-Jul-2023

GENERAL COMMENTS	<p>- citation: 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%: do you mean the median of the duration of the disease?</p> <p>Do you consider presenting in the discussion the podiatric approach to the treatment of onychomycosis and the multidisciplinary vision with the insertion of specialized professionals for this work, such as podiatrists and specialist nurses?</p> <p>Another issue is the quote from the IWGDF World Consensus?</p>
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	My suggestion and opinion is that they are important aspects for defining public policies in primary health care. needed a hospital referral after a median of 7.4 years (IQR 9.2).
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REVIEWER	Wu, Yue East China University of Science and Technology, School of Information Science and Engineering
REVIEW RETURNED	05-Sep-2023

GENERAL COMMENTS	The reviewer's key concerns are as following: (1) The manuscript does not include a CONSORT, STROBE or PRISMA checklist. Please reorganize the data analysis section with a participant flow chart detailing the grouping of cases. (2) It is unclear if the control group is fair. Were other conditions equal between the onychomycosis patients and controls? (3) Onychomycosis is mainly caused by environmental factors. Related research shows nursing practices and lifestyle have a large impact on ulcer formation. The study only considered treatment as a confounding factor. Were other confounding factors considered, like patient exposure to damp environments, unclean socks/shoes causing onychomycosis and in turn ulcer formation? This needs to be reflected in the results and discussion.
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REVIEWER	Zhao, Yang China Academy of Chinese Medical Sciences Xiyuan Hospital
REVIEW RETURNED	18-Sep-2023

GENERAL COMMENTS	1. Incomplete description of demographic information 2. Inadequate statistical analysis of primary outcome
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VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' comments to author:

Reviewer: 1 Dr. María Gabriela Morgado Tapia, Universidad Andres Bello

Comments to the Author:

1. The study doesn't declare how it accessed the data and how its confidentiality was protected, under local regulations.

a. Reply: Thank you for your comment, we have added the requested information.

b. Changes in the manuscript: On page 5 under the subheading 'Data and setting' we have rewritten part of the text and added information (highlighted in yellow) to clarify that we were merely provided with the requested dataset being extracted from the ELAN database without the investigators having access to the ELAN database itself.

2. It's necessary to update references. Most of them are over 10 years old.

a. Reply: Thank you for your valid comment.

b. Changes in the manuscript: The references were updated. We removed non-essential and outdated references and replaced them where necessary (see updated reference list). A few older studies on onychomycosis represent evidence that has not been reproduced more recently, hence we felt these needed to remain.

3. It is recommended to review the description of statistical analysis

a. Reply: Thank you for your recommendation.

b. Changes in the manuscript: We have reviewed the paragraph on statistical analyses and added additional explanation (p7, highlighted in yellow) to emphasize the time-dependent aspect of the cox-proportional hazards models and to clarify that there were three models constructed for each of the outcomes, required to answer our research questions.

Reviewer: 2 Dr. Bassey E. Ekeng, Medical Mycology Society of Nigeria

Comments to the Author:

This is a great work. However do upgrade the section on introduction.

The study design seems retrospective. Kindly ratify as per the appended comments

a. Reply: Thank you for your compliment, very much appreciated. We upgraded the section on introduction by updating the references, as also suggested by reviewer 1, mainly concerning the introduction. Regarding the study design, we agree with the reviewer that this study design is retrospective. Due to ongoing debate about whether or not to use the term retrospective, we initially chose the term longitudinal instead. As we do agree, we added the term retrospective.

b. Changes in the manuscript: retrospective study design added on p5, highlighted in yellow.

Please also see attached comments

a. Reply: Thank you for your comments. We have addressed all comments in our manuscript, by copying the comment from the pdf to our Word file and providing our answer (see marked copy).

b. Changes in the manuscript: The corresponding changes within the manuscript are highlighted in yellow on p4.

Reviewer: 3 Dr. Monica Antar Gamba, Universidade Federal de São Paulo

Comments to the Author:

- citation: 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). Do you mean the median of the duration of the disease?

a. Reply: Thank you for your comment. That is correct, the times mentioned in this section refer to the time between the diagnosis of DM (i.e. the start of our follow-up period) and the event occurring.

b. Changes to the manuscript: none applicable.

- Do you consider presenting in the discussion the podiatric approach to the treatment of onychomycosis and the multidisciplinary vision with the insertion of specialized professionals for this work, such as podiatrists and specialist nurses?

a. Reply: Thank you for this valid comment. We fully endorse the multidisciplinary approach to diabetes care and diabetic foot care in particular, including the importance of specialized professionals such as podiatrists and specialized nurses. This is already implemented in the current Dutch healthcare system.

b. Changes to the manuscript: As the value of this multidisciplinary approach and the insertion of specialized professionals were unfortunately not part of our research, having no reliable data on these important aspects, we feel that adding this topic to the discussion can unfortunately not be fully justified since we were limited to merely the study of the associations described.

- Another issue is the quote from the IWGDF World Consensus? My suggestion and opinion is that they are important aspects for defining public policies in primary health care.

a. Reply: Thank you for this important comment. We also fully support the IWGDF World Consensus and the IWGDF guidelines that are incorporated into our national and local guidelines, both in primary and secondary care.

b. Changes to the manuscript: In the updated references, we now specifically refer to the important statement and guideline from the IWGDF in our Introduction section (reference 6).

Reviewer: 4 Dr. Yue Wu, East China University of Science and Technology

Comments to the Author:

The reviewer's key concerns are as following:

(1) The manuscript does not include a CONSORT, STROBE or PRISMA checklist. Please reorganize the data analysis section with a participant flow chart detailing the grouping of cases.

a. Reply: Thank you for your important remark. We did have a checklist but apparently, it did not upload correctly. We have added the corresponding STROBE checklist. Regarding the data analysis section, we feel a flowchart would not be suitable in this context as it would imply that we actively would have defined two or more groups from the start. Following our type of survival analysis, we merely observed the exposures and events over time within all diabetic patients. At baseline i.e. the start of follow-up, there were no two different groups, only one big group of diabetic patients who did or did not develop onychomycosis, and did or did not develop an ulcer. A flowchart would imply active grouping from baseline, which was not the case.

b. Changes to the manuscript: n.a.

(2) It is unclear if the control group is fair. Were other conditions equal between the onychomycosis patients and controls?

a. Reply: Thank you for your important remark. In line with the explanation above, there was no grouping or matching between cases and controls; the start of follow-up was merely the date of diagnosis of DM, and the whole group was the same in that sense. Therefore, there was no difference between these groups at baseline, and comparing their conditions at baseline would imply a kind of matching which was not the case.

b. Changes to the manuscript: n.a.

(3) Onychomycosis is mainly caused by environmental factors. Related research shows nursing practices and lifestyle have a large impact on ulcer formation. The study only considered treatment as a confounding factor. Were other confounding factors considered, like patient exposure to damp environments, unclean socks/shoes causing onychomycosis and in turn ulcer formation? This needs to be reflected in the results and discussion.

a. Reply: Thank you for this important remark. We are aware that lifestyle and nursing practices have a large impact, as well as other factors such as a damp environment or unclean socks/shoes. Not only did we consider antimycotic treatment as a confounding factor, but all the risk factors that were available to us in our data. They are mentioned in the legend of Table 3 (after the asterisk) and also described on page 6. All confounders available to us were adjusted for in the final multivariate model. Unfortunately, we did not have any data on exposure to a damp environment, unclean socks, or other factors that were not registered in our data, hence we were unable to add these to our analyses.

b. Changes to the manuscript: n.a.

Reviewer: 5 (Dr. Yang Zhao, China Academy of Chinese Medical Sciences Xiyuan Hospital)

Comments to the Author:

1. Incomplete description of demographic information

a. Reply: Thank you for your comment. We agree that the demographic information displayed in Table 1 is limited. Unfortunately, these were the only demographic data available to us from the ELAN data source. In addition, although displayed in a different table (Table 2), we did have more extensive data to describe our population. However, due to the nature of the statistical analyses required to answer our research questions, we felt it more suitable to provide this information in a separate table (Table 2) to indicate these data as exposures and events/outcomes.

b. Changes to the manuscript: n.a.

2. Inadequate statistical analysis of primary outcome

a. Reply: Thank you for your comment. Due to the complex nature of this type of survival analysis, the data cleaning, the selection of the correct statistical method, the actual performance of analyses, and the review of the final results, were all done under the supervision of an experienced statistician. Therefore, we feel the chosen analyses are suitable to answer our research question and are representative of this type of study.

b. Changes to the manuscript: n.a.

VERSION 2 – REVIEW

REVIEWER	Tapia, María Gabriela Morgado Universidad Andres Bello, Nursing Faculty
REVIEW RETURNED	24-Oct-2023
GENERAL COMMENTS	Changes introduced are adequate to prior review.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1 Dr. María Gabriela Morgado Tapia, Universidad Andres Bello

1. Changes introduced are adequate to prior review

- Reply: Thank you for your comment, we are very glad to hear.
- Changes to the manuscript: not applicable