

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Cohort profile: The ReLife (Renal cell cancer: Lifestyle, prognosis, and quality of life) study in the Netherlands
AUTHORS	Maurits, Jake; Sedelaar, Michiel; Aben, Katja; Kampman, Ellen; Kiemeneij, Lambertus; Vrieling, Alina

VERSION 1 – REVIEW

REVIEWER	Ashika Maharaj TU Delft, Faculty of Technology, Policy and Management
REVIEW RETURNED	11-Jan-2023

GENERAL COMMENTS	<p>Maurits et al have provided a cohort profile on the ReLife study to be conducted in the Netherlands. The aims and objectives of the study are interesting and the methods are clearly presented. However, for this study to be described as a cohort profile, do the authors plan to collect information longitudinally beyond 2 years (time-limited)? Please check author instructions of the BMJ Open which states "Cohorts described should be long-term, prospective projects and not time-limited cohorts established to answer a small number of specific research questions. Papers addressing a specific research question using cohort data should be submitted as a Research paper."</p> <p>Some other areas to be addressed:</p> <ul style="list-style-type: none">- objectives are clearly defined but authors may consider moving the objectives from the 'settings' section in the methods to the end of the introduction to provide better flow for the readers.- consider defining the terminology 'clinical outcomes' in the introduction. Do the authors mean survival, mortality, treatment effectiveness..? To some extent, this has been addressed in the methods (line 236).- the authors present statistics on worldwide kidney cancer cases. As the study is conducted in the Netherlands, what is the estimated number diagnosed with RCC in the country per year? This maybe helpful to assess representation/population coverage of the cohort to some extent.- Urologists were asked to 'select and invite eligible patients' - What was the inclusion / exclusion criteria for the urologists? Further on, the authors mention eligible participants were Dutch speaking which poses the question whether urologists were asked to exclude non-Dutch speaking participants. This is an important consideration for the limitations section. It is also then unclear in which language the questionnaires were distributed e.g. EORTC QLQ C30.- In the findings to date, authors mention that "participants were comparable to non-participants...." How was this determined and how many non-participants were compared? Was a Chi-squared test
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	<p>undertaken for this comparison - if so, this should be briefly described in the data analysis section and significance levels provided based on the analysis in the findings to date. Also, have the authors considered the software that will be used for further analysis (R, STATA, SPSS?) and should include in the data analysis section.</p> <p>-In the findings to date, the authors present data on initial recruitment, and patient demographics. It is also mentioned, that data collection at 3 months and 1 year post diagnosis has been finalised. Are there any early trends based on this data that can be shared and would be of interest to the readers? This could include time taken to complete and satisfaction with the questionnaires/survey... e.g. is there any indication that the participants were happy to complete a 163 item questionnaire on diet plus the other questionnaires? Was data burden a limitation? Timing of questionnaire completion.. At the very least, some of these points can be discussed in the limitations section.</p> <p>- section on collaboration (as per the author instructions for BMJ Open cohort profile) is missing</p> <p>- strengths and limitations of the study should be expanded and discussed in depth within the body of the manuscript (not just the bullet points following the abstract).</p> <p>- discussion on the implications of this research would be useful.</p>
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REVIEWER	Wei Wang Beijing Chaoyang Hospital
REVIEW RETURNED	19-Jan-2023

GENERAL COMMENTS	<p>Thank you very much for inviting me to peer review this article. This study is a prospective cohort study based on the currently suspected prognostic factors of patients with localized renal cell carcinoma to explore the relationship between lifestyle and quality of life in patients with renal cell carcinoma. Unfortunately, I don't think the results of this paper are qualified for publication. It is macroscopical that this study has not been completed so far. Although the author describes the overall research background, purpose and research plan in great detail, the current available research results can not solve the original goal of this study. It is undeniable that if this study is completed in the future, authors will get a more convincing conclusion.</p>
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REVIEWER	Kgomotso Mathabe University of Pretoria
REVIEW RETURNED	23-Jan-2023

GENERAL COMMENTS	<p>This was a lovely study and a lovely paper to review.</p> <p>Checklist points 1- 5 The research question, abstract, study design, methods, research ethics are appropriate for the actual study where the results are analysed relative to the research question/ aim of the study. Which study this manuscript is introducing, not reporting.</p> <p>Checklist point 6 The outcomes of the main analytical study are clearly defined, but are not presented in this descriptive study of the cohort profile.</p> <p>Checklist point 7 The results are not being presented in this manuscript, as data</p>
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	<p>collection is still being conducted and thus data analysis is not yet done.</p> <p>Checklist point 9 & 10 The results that are being described, those of the profile of the cohort are clear.</p> <p>Checklist point 11 While data collection and analysis are ongoing and in the absence of inferential/ analytical statistics, the absence of a discussion and conclusion are appropriate.</p> <p>Checklist point 12 Yes.</p> <p>Checklist point 13 N/A.</p> <p>Checklist point 14 Yes.</p> <p>Checklist point 15 Minor editorial/ grammatical corrections to be made.</p> <p>Additional comments</p> <p>Abstract</p> <ul style="list-style-type: none"> • Line 31, the word including is better replaced with involving. • Line 36, the word donate is not the best fit. This may be a regional nuance, but giving blood for compulsory testing in a study is not a donation, even if it is with consent. • Line 42, as recruitment/ enrolment is completed, better to add the word were in front of included (response rate 44%) • Line 47 on the 3 month and 1-year data collection being finalised is probably better placed under findings to date, rather than future plans. • Line 55, replace were with is, as the data collection is still ongoing. • Line 56, depending on how temporally related the diagnosis and treatments are, the authors may want to change from diagnosis to treatment, as all along it has been specified that the visits for data collection are at a time period after treatment. • Line 57, body composition as described cannot be self-reported. Rather self-reported data on physical activity and objective data on body composition were collected. <p>Introduction</p> <ul style="list-style-type: none"> • The introduction makes a strong case for why the study is being conducted. • Line 63, perhaps add a line about how the worldwide figures may be an underestimate as cancer reporting and registries are incomplete in certain parts of the world. • Line 85 about the counterintuitive finding is powerful. • Calling the study essential (line 49 and line 118) feels like overreaching, perhaps just call it important. Some of the factors studied here may in time prove to not be essential or useful to personalising lifestyle advice to improve clinical outcomes. • Presentation of ethnicity data would strengthen the case for demographic data being collected and address the point made about reported differences in body composition on the basis of race (line 104). Do different ethnicities show the same linear relation with body
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	<p>TAT and SM mass? If not, then a line should probably be added on this ethnic difference.</p> <p>Cohort description</p> <ul style="list-style-type: none"> • Line 143, this line reads better as patients were not involved in conducting this research (as it stands it is not incorrect.) • Line 151, a case isn't made for why participants had to be Dutch-speaking, so perhaps just say Dutch patients (which addresses Dutch residence without any further prejudicial aspects of nationality or citizenship. Finer analysis can refer to the participants self-reported ethnicity as and when needed.) • Line 160, labelling the time frames for assessment with a T in a study on cancer where T refers to tumour characteristics is confusing, and thus an alternative letter should be considered for example V3mo for visit at 3 months. • Line 172, either write as ... SQUASH which is reliable, if it is. Or refer only to the validity if that's all that is available. Fairly reliable raises concern. • Line 192, converted may work better than transformed. • Line 217, assuming local pathology lab specimens are preserved in formalin, rather than being frozen? If so, please specify. For genetic studies snap-frozen material provides a higher yield, thus assessment for acquired genetic alterations may give suboptimal results based on the preservation method of the tissues rather than any biological reason. • Line 273, reads grammatically correctly as the majority of participants were (not was) overweight or obese and half were former smokers. • A line about why not all the demographic data collected is not being included in this description of the cohort such as ethnicity, living situation, occupation, mental status, alcohol use and physical activity, would be nice Alternatively an inclusion of those variables. <p>Table 2, perhaps place n (%) in the top line of the table to cover all the subsequent variables presented, instead of next to each individual variable.</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Mrs. Ashika Maharaj, Monash University

Comments to the Author:

Maurits et al have provided a cohort profile on the ReLife study to be conducted in the Netherlands. The aims and objectives of the study are interesting and the methods are clearly presented. However, for this study to be described as a cohort profile, do the authors plan to collect information longitudinally beyond 2 years (time-limited)? Please check author instructions of the BMJ Open which states "Cohorts described should be long-term, prospective projects and not time-limited cohorts established to answer a small number of specific research questions. Papers addressing a specific research question using cohort data should be submitted as a Research paper."

Although this had not been clearly stated in the first version of our manuscript, we do indeed plan to collect information longitudinally beyond 2 years. This will concern information regarding tumour recurrence, progression and survival. We have now added this information to the manuscript. Thereby, we think this manuscript fulfils the criteria for a cohort profile.

Line 49: "Data collection at 2 years after treatment is expected to be finalized in June 2023 and longitudinal clinical data will continue to be collected."

Line 259: "We will continue to collect further information on these clinical outcomes in the future to evaluate their association with body composition features, lifestyle habits and circulating biomarkers."

Some other areas to be addressed:

- objectives are clearly defined but authors may consider moving the objectives from the 'settings' section in the methods to the end of the introduction to provide better flow for the readers.

We thank the reviewer for this suggestion and have now moved the objectives from the 'settings' section in the methods to the end of the introduction.

- consider defining the terminology 'clinical outcomes' in the introduction. Do the authors mean survival, mortality, treatment effectiveness..? To some extent, this has been addressed in the methods (line 236).

We have defined the terminology 'clinical outcomes' at the end of the introduction as 'postoperative outcomes (e.g. complications, length of hospital stay), recurrence, progression, survival, and HRQOL'.

Line 136: "the association of body composition features, lifestyle habits and circulating biomarkers with clinical outcomes, including postoperative outcomes (e.g. complications, length of hospital stay), recurrence, progression, survival, and HRQOL."

- the authors present statistics on worldwide kidney cancer cases. As the study is conducted in the Netherlands, what is the estimated number diagnosed with RCC in the country per year? This may be helpful to assess representation/population coverage of the cohort to some extent.

We thank the reviewer for this suggestion and have now added the estimated number diagnosed with RCC in The Netherlands.

Line 67: "In the Netherlands, over 2,700 new cases with kidney cancer were diagnosed in 2019 (4)."

- Urologists were asked to 'select and invite eligible patients' - What was the inclusion / exclusion criteria for the urologists? Further on, the authors mention eligible participants were Dutch speaking which poses the question whether urologists were asked to exclude non-Dutch speaking participants. This is an important consideration for the limitations section. It is also then unclear in which language the questionnaires were distributed e.g. EORTC QLQ C30. This may not have been stated clearly enough but urologists did not select and invite eligible patients but they were asked for permission to have their eligible patients selected and invited from the Netherlands Cancer Registry by personnel from the Netherlands Comprehensive Cancer Organisation. We have now revised this.

Line 132: "Before the start of the study, permission was asked from all urologists of the participating hospitals to select and invite eligible patients from the Netherlands Cancer Registry (NCR), held by the Netherlands Comprehensive Cancer Organisation (IKNL). Once every 2 weeks, newly diagnosed patients were identified by IKNL personnel using notification lists of the Pathological Anatomical National Automate Archive (PALGA foundation) in the Netherlands. Approximately 10 weeks after treatment (surgery or ablation), patients were invited by IKNL personnel on behalf of their urologist to participate in this study (Figure 1)."

We have now added that all study materials and questionnaires were in Dutch. Patients who did not have sufficient command of the Dutch language were excluded since they were not able to sufficiently understand the study materials and questionnaires.

Line 155: "Eligible participants were between 18 and 75 years old who were newly diagnosed with a histologically confirmed primary stage I-III RCC tumour and who underwent a (partial) nephrectomy or ablation. Patients had to have sufficient command of the Dutch language since all study materials and questionnaires were only available in Dutch."

- In the findings to date, authors mention that "participants were comparable to non-participants...." How was this determined and how many non-participants were compared? Was a Chi-squared test undertaken for this comparison - if so, this should be briefly described in the data analysis section and significance levels provided based on the analysis in the

findings to date. Also, have the authors considered the software that will be used for further analysis (R, STATA, SPSS?) and should include in the data analysis section.

Patient characteristics of all participants (n=368) were compared to those of all non-participants (n=468) using Chi-squared tests. All statistical analyses will be conducted in R. We have now added the following information to the “Data analysis” section.

Line 275: “Patient characteristics were described using means and standard deviations (SD), medians and interquartile ranges (IQR), or total numbers and percentages where appropriate. Differences in sociodemographic and clinical characteristics between participants and non-participants were evaluated with chi-squared tests.”

Line 284: “All statistical analyses will be conducted in R.”

We have also included these results in a new table (Table 3). We only observed a difference in sex with participants being more likely to be female than non-participants but not in age, tumour stage, Fuhrman grade, morphology and type of treatment.

-In the findings to date, the authors present data on initial recruitment, and patient demographics. It is also mentioned, that data collection at 3 months and 1 year post diagnosis has been finalised. Are there any early trends based on this data that can be shared and would be of interest to the readers? This could include time taken to complete and satisfaction with the questionnaires/survey... e.g. is there any indication that the participants were happy to complete a 163 item questionnaire on diet plus the other questionnaires? Was data burden a limitation? Timing of questionnaire completion.. At the very least, some of these points can be discussed in the limitations section.

Data collected at 1 year postdiagnosis have not yet been cleaned and analysed. Therefore, we cannot include this information in this manuscript yet and cannot share any early trends. This will be part of a results paper to be submitted in the future. We did not collect information on time taken to complete and satisfaction with the questionnaires so we cannot report on this either. We do have information on timing of questionnaire completion. Median time between time of treatment and time of the 3mo questionnaire completion was 13 weeks (interquartile range 12-14 weeks). We have now added this information to the “Findings to date” section.

Line 295: “The median time between time of treatment and time of the 3mo questionnaire completion was 13 weeks (interquartile range 12-14 weeks).”

- section on collaboration (as per the author instructions for BMJ Open cohort profile) is missing

We thank the reviewer for pointing this out since we had completely overlooked that this section was required. We have now added a section on collaboration.

Line 364: “COLLABORATION

The ReLife study group is open for collaborations with national and international colleagues. Any person interested in collaborating on the ReLife study or in getting access to ReLife data for data analyses can contact the corresponding author. Requests for data will be discussed and decided by the ReLife study group and will require a Data Transfer Agreement.”

- strengths and limitations of the study should be expanded and discussed in depth within the body of the manuscript (not just the bullet points following the abstract).

We thank the reviewer for pointing this out since we had completely overlooked that this section was required. We have now added a discussion of the strengths and limitations of the study to the body of the manuscript.

Line 342: “STRENGTHS AND LIMITATIONS

To our knowledge, the ReLife study is the first population-based prospective longitudinal study on lifestyle-related factors and clinical outcomes in patients with localized RCC worldwide.

Comprehensive data on lifestyle-related factors and HRQOL are collected at 3 months, 1 year and 2 years after treatment. Besides questionnaire data on lifestyle-related factors, also objective data on body composition and physical activity are collected. Data on sociodemographic variables and

comorbidity is available as well. Information on several clinical outcomes is collected, including postoperative outcomes (e.g. complications, length of hospital stay), recurrence, progression, survival, and HRQOL. Moreover, blood samples are collected to measure lifestyle-related, disease-related and genetic biomarkers. Permission is available from participants to use their tumour tissue blocks for assessment of tumour characteristics and acquired genetic alterations. However, there are also some limitations to this study. As is the case for all longitudinal studies, participants may drop out during the course of the study, potentially leading to selection bias. Some variables have missing values which will be addressed using multiple imputation when applicable. No information on lifestyle-related factors and HRQOL after the two-years follow-up measurement is available. Power for survival analyses is likely to be insufficient and future pooling with other studies may be necessary. Lastly, we did not use RCC-specific measures of HRQOL in our study.”

- discussion on the implications of this research would be useful.

We have now added the following information to the Strengths and Limitations:

Line 361: “Results that can be obtained from this study are important to develop personalized evidence-based lifestyle advice for patients with localized RCC to improve their clinical outcomes.”

Reviewer: 2

Dr. Wei Wang, Beijing Chaoyang Hospital

Comments to the Author:

Thank you very much for inviting me to peer review this article. This study is a prospective cohort study based on the currently suspected prognostic factors of patients with localized renal cell carcinoma to explore the relationship between lifestyle and quality of life in patients with renal cell carcinoma. Unfortunately, I don't think the results of this paper are qualified for publication. It is macroscopical that this study has not been completed so far. Although the author describes the overall research background, purpose and research plan in great detail, the current available research results cannot solve the original goal of this study. It is undeniable that if this study is completed in the future, authors will get a more convincing conclusion.

We agree with the reviewer that the currently available research results cannot yet solve the original goal of this study. However, that is also not the intention of the current manuscript. The following information regarding a cohort profile is stated in the information for authors; “The cohort profile is an article type set up in BMJ Open to fill the space between a study protocol and a results paper. Cohort profiles should describe the rationale for a cohort's creation, its methods, baseline data and its future plans. Cohorts described should be long-term, prospective projects and not time-limited cohorts established to answer a small number of specific research questions.”

In our opinion, our manuscript fulfils the criteria of a cohort profile. It is not intended to be a results paper. Therefore, the results of this manuscript only include a description of the baseline data. Results papers will follow in the future once data collection up to 2 years after diagnosis has been completed.

Reviewer: 3

Dr. Kgomotso Mathabe, University of Pretoria

Comments to the Author:

This was a lovely study and a lovely paper to review.

We thank the reviewer for this positive feedback.

Checklist points 1- 5

The research question, abstract, study design, methods, research ethics are appropriate for the actual study where the results are analysed relative to the research question/ aim of the study. Which study this manuscript is introducing, not reporting.

No response required.

Checklist point 6

The outcomes of the main analytical study are clearly defined, but are not presented in this descriptive study of the cohort profile.

No response required.

Checklist point 7

The results are not being presented in this manuscript, as data collection is still being conducted and thus data analysis is not yet done.

No response required.

Checklist point 9 & 10

The results that are being described, those of the profile of the cohort are clear.

No response required.

Checklist point 11

While data collection and analysis are ongoing and in the absence of inferential/ analytical statistics, the absence of a discussion and conclusion are appropriate.

No response required.

Checklist point 12

Yes.

No response required.

Checklist point 13

N/A.

No response required.

Checklist point 14

Yes.

No response required.

Checklist point 15

Minor editorial/ grammatical corrections to be made.

We have made the editorial/grammatical corrections indicated below.

Additional comments**Abstract**

- **Line 31, the word including is better replaced with involving.**

Done.

- **Line 36, the word donate is not the best fit. This may be a regional nuance, but giving blood for compulsory testing in a study is not a donation, even if it is with consent.**

We have replaced this by "have blood samples taken".

- **Line 42, as recruitment/ enrolment is completed, better to add the word were in front of included (response rate 44%)**

Done.

- **Line 47 on the 3 month and 1-year data collection being finalised is probably better placed under findings to date, rather than future plans.**

Done.

- **Line 55, replace were with is, as the data collection is still ongoing.**

Done.

- **Line 56, depending on how temporally related the diagnosis and treatments are, the authors may want to change from diagnosis to treatment, as all along it has been specified that the visits for data collection are at a time period after treatment.**

We thank the reviewer for pointing out this inconsistency. We now refer to all timepoints as 'after treatment'.

- **Line 57, body composition as described cannot be self-reported. Rather self-reported data on physical activity and objective data on body composition were collected.**

Body mass index and waist and hip circumference are also (less specific) measures of body composition. Therefore, we prefer to leave this text like it is.

Introduction

- **The introduction makes a strong case for why the study is being conducted.**

We thank the reviewer for these kind words.

- **Line 63, perhaps add a line about how the worldwide figures may be an underestimate as cancer reporting and registries are incomplete in certain parts of the world.**

We acknowledge that this may be the case but we think that adding this is too much detail for this general introduction. Instead, we have added the incidence for The Netherlands which has a complete cancer registry, according to the suggestion of reviewer 1.

Line 67: "In the Netherlands, over 2,700 new cases with kidney cancer were diagnosed in 2019 (4)."

- **Line 85 about the counterintuitive finding is powerful.**

We thank the reviewer for these kind words.

- **Calling the study essential (line 49 and line 118) feels like overreaching, perhaps just call it important. Some of the factors studied here may in time prove to not be essential or useful to personalising lifestyle advice to improve clinical outcomes.**

We have replaced essential with important.

- **Presentation of ethnicity data would strengthen the case for demographic data being collected and address the point made about reported differences in body composition on the basis of race (line 104). Do different ethnicities show the same linear relation with body TAT and SM mass? If not, then a line should probably be added on this ethnic difference.**

We have added information on ethnicity to Table 2. In our cohort, 97% of participants were White. For the remainder, ethnicity was Black (0.3%), Asian (1%), other (1%) or missing (1%). The linear relation with body TAT and SM mass has also been shown for mixed study populations consisting of Caucasian, African American, Hispanic, Asian, and other ethnicities.

Cohort description

- **Line 143, this line reads better as patients were not involved in conducting this research (as it stands it is not incorrect.)**

We have replaced this by "Patients were not involved in the conduction of this research".

- **Line 151, a case isn't made for why participants had to be Dutch-speaking, so perhaps just say Dutch patients (which addresses Dutch residence without any further prejudicial aspects of nationality or citizenship. Finer analysis can refer to the participants self-reported ethnicity as and when needed.)**

To clarify why participants had to be Dutch-speaking, we have added here that all study materials and questionnaires were only available in Dutch.

Line 155: "Eligible participants were between 18 and 75 years old who were newly diagnosed with a histologically confirmed primary stage I-III RCC tumour and who underwent a (partial) nephrectomy or ablation. Patients had to have sufficient command of the Dutch language since all study materials and questionnaires were only available in Dutch."

- **Line 160, labelling the time frames for assessment with a T in a study on cancer where T refers to tumour characteristics is confusing, and thus an alternative letter should be considered for example V3mo for visit at 3 months.**

We have removed all T's for the assessment, so we are now referring to 3mo, 1y and 2y.

- **Line 172, either write as ... SQUASH which is reliable, if it is. Or refer only to the validity if that's all that is available. Fairly reliable raises concern.**

We have rephrased this as: "Information about habitual physical activity is collected by using the validated short questionnaire to assess health-enhancing physical activity (SQUASH) (37)."

- **Line 192, converted may work better than transformed.**

Since transformed is used in most other papers on the EORTC QLQ-C30, we prefer to keep this like it is.

- **Line 217, assuming local pathology lab specimens are preserved in formalin, rather than being frozen? If so, please specify. For genetic studies snap-frozen material provides a higher yield, thus assessment for acquired genetic alterations may give suboptimal results based on the preservation method of the tissues rather than any biological reason.**

We have added that this concerns formalin-fixed paraffin-embedded tumour blocks.

- **Line 273, reads grammatically correctly as the majority of participants were (not was) overweight or obese and half were former smokers.**

We have replaced this by; “The majority of participants were overweight (44%) or obese (25%) and 50% were former smokers.”

- **A line about why not all the demographic data collected is not being included in this description of the cohort such as ethnicity, living situation, occupation, mental status, alcohol use and physical activity, would be nice. Alternatively an inclusion of those variables.**

We have now added information about ethnicity, living situation, occupation, alcohol use and physical activity. We assume that with mental status the reviewer is referring to quality of life. Since this is one of our outcomes, we prefer to publish about that in a results paper.

Table 2, perhaps place n (%) in the top line of the table to cover all the subsequent variables presented, instead of next to each individual variable.

We have now removed all n (%) and mean ± SD, and have added a footnote stating “Values are mean ± SD or n (%)”.

VERSION 2 – REVIEW

REVIEWER	Ashika Maharaj TU Delft, Faculty of Technology, Policy and Management
REVIEW RETURNED	04-Mar-2023

GENERAL COMMENTS	I commend the authors on addressing my initial concerns with their manuscript and wish them well for data collection and analysis/reporting of findings.
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REVIEWER	Kgomotso Mathabe University of Pretoria
REVIEW RETURNED	05-Mar-2023

GENERAL COMMENTS	The efforts of the authors to amend are recognised. In line 280 it says 70% of participants were male. Then line 283 says participants were more likely to be female than non-participants. Non-participants shouldn't be discussed in the study. I'm not sure if this is perhaps in making a distinction between study subjects and controls.
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