OBSTETRICS & GYNECOLOGY

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- Comments from the reviewers and editors (email to author requesting revisions)
- Response from the author (cover letter submitted with revised manuscript)*

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Date: Apr 02, 2021
To: "Jeppe Bennekou Schroll" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-21-122

RE: Manuscript Number ONG-21-122

Human papillomavirus testing in the last cervical screening round at age 60-64: Register-based study

Dear Dr. Schroll:

Your manuscript has been reviewed by the Editorial Board and by special expert referees. Although it is judged not acceptable for publication in Obstetrics & Gynecology in its present form, we would be willing to give further consideration to a revised version.

If you wish to consider revising your manuscript, you will first need to study carefully the enclosed reports submitted by the referees and editors. Each point raised requires a response, by either revising your manuscript or making a clear and convincing argument as to why no revision is needed. To facilitate our review, we prefer that the cover letter include the comments made by the reviewers and the editor followed by your response. The revised manuscript should indicate the position of all changes made. We suggest that you use the "track changes" feature in your word processing software to do so (rather than strikethrough or underline formatting).

Your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Apr 23, 2021, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1:

Overall: Important topic, relevant to our current process change related to incorporating HPV for primary cervical cancer screening.

Abstract: clear and well written
Introduction: Generally some grammatical and flow issues that I would recommend editing. Otherwise content is appropriate. The aims could be more completely stated, a bit vague as written.
Methods:
* The first paragraph is very confusing. This description might work well if the reader was more knowledgeable about the system in Denmark, but I am uncertain what a "personal invitation" is. By mail? Electronically?
* Also, Lines 102-105 don't seem appropriate for the methods section.
* I don't know what "well-screened" means - should be defined.
* There is considerable variation between regions, which is somewhat confusion.
* When noted "discharged for the program" was that anyone between 60-64?
* The paragraph between lines 155-172 is extremely confusing. This paragraph needs to be reworked, or broken into several paragraphs to make the content clearer.
Results: Clear and well written
Discussion:
* Lines 258-271: Some component of this should be outlined in the methodology.
* Lines 273-277: Should be incorporated elsewhere, does not stand alone.
* Overall, the discussion is very verbose and a bit jumbled. It was hard to follow.
* There is a comprehensive discussion of the limitations, but I think these could be consolidated and presented in a more concise manner. Perhaps some of the background information could be better incorporated into the introduction.

Reviewer #2:

This is large population based observation al study to evaluate the outcomes of adding HPV testing to the "exist" screening visit for cervical cancer in women 60-64 years compared to other methods of screening

Main issues:
1- The heterogeneity of the different protocol and the small number of outcomes which is expected are important factors that affect the reliability of this study as well as other studies evaluating cervical cancer screen. Still, this is a large database that is population based. How did the authors account for this heterogeneity and how much did this affect the results?
2- For the number of positive testing and CIN2 and CIN3, did the author adjust for known risk factors?

Specific issues:
1- Methods:
a. Did the authors consider any sample size estimation and what is the primary outcome of this study? Please include the primary outcome
b. Did the author considered regression analysis to adjust for known risk factors?
c. Did the author consider CIN2 and CIN3 as the outcome of study rather than cervical cancer and did they adjust for known risk factors? Did the author use proportional hazard modeling to adjust for potential confounders?
2- Results:
a. What was the follow up duration and is it different between the 2 groups, please add to table 2. Did the author limit the follow up to certain time in both groups?
b. Please add another figure with CIN2 and CIN3 as the primary outcome for a survival analysis.
c. To address heterogeneity, using a multivariate proportional hazard model might help
3- Discussion:
a. Can be shorter
b. Please compare the incidence of CIN2 and 3 in this study with the prior 4 RCTS that did not detect a difference in the cervical cancer detection rate.

Reviewer #3:

This study is a retrospective analysis of the implementation of primary HPV screening compared with previous cytology based cervical cancer screening in the age group of woman exiting from screening. Methods and outcomes are well described. Impacts of HPV testing on screen positive rates, detection of high grade dysplasia and cancers and number of colposcopies and potential surgical procedures are well described. This paper highlights many of the issues of primary HPV testing in this age group and the challenges of when and how to exit cervical cancer screening. Some of this paper's findings have previously been published but in smaller numbers of women. What is unique to this paper is the large number of women from a population database. As the appropriate age to stop cervical cancer screening is unclear it is important to have papers like this, which document advantages and disadvantages of different exit screening tests. The short term follow up of significant disease is also informative but longer term data is needed.

How did your study distinguish when labs were doing primary HPV testing verses primary cytology with HPV triage? Was it based on particular HPV assay? For example in Table 1 the Capital region was using Hybrid capture until Oct 2014 yet HPV period analysis started August 2014 - was the hybrid capture2 test used for primary HPV testing? As hybrid capture 2 is usually used for reflex/triage or contesting and not primary HPV testing?

Did individual labs have times during transition where they were doing both primary HPV and cytology screening or did they abruptly transition and do only primary HPV testing with cytology triage and no more cytology screening? You describe that happening with opportunistic verses invited screening tests but it was unclear if there was an overlap period even for invited tests. Did any of the labs ever do cotesting?

In the patients with screen negative testing and subsequent cervical cancer diagnosis could their previous screening histories prior to age 60 be reported? It would be useful to know if they had been well screened up to that point and if they had any abnormal cytology in the decade before they were to exit screening.

Line 165 defined primary screening - if no cervical record prior 2 years. Is it possible some woman with recently detected HSIL or treated high grade CIN might miss a year or two of follow up? Could your database be queried for CIN diagnosed in the past decade and possibly analyze these women differently than the "low" risk women who should be exiting screening?

Table 2. Why were the 17% with cytology from opportunistic tests included in HPV period? It would be best to also report the analysis with these results removed.

Line 358 - "substituting cytology for HPV"- this seems confusing as you are substituting HPV for cytology.

There are several studies from Sweden that look at women 60 years and older having primary HPV, with some comparison

to cytology screening. These studies are relevant to your study and should be discussed.

STATISTICS EDITOR COMMENTS:

Abstract: Should include the number of women and women-years in each cohort. See later comments re: The risk rate cited.

Table 2: While this Table is informative, should also include a flow diagram following the explanation for the two cohorts as on lines 198-204. For the HPV period cohort, begin with 54397, subtract 343 as inadequate test, then have 54054 remaining. Of those, 2891 had (+) screen, of those 2739 (94.7%) had follow-up, of those, 1770 (64.6%) had colposcopy, of those, 1503 (84.9%) had < CIN2, 267 (15.1% had CIN2+ etc. Then show corresponding counts and % for the cytology period cohort. I think that this would make the proportions less confusing for the reader.

lines 226-230: Using the data provided, I obtained a slightly different RR 0.99 (95% CI 0.42-2.35). Please verify your calculations. Also, given the number of patients and the counts for women-years in each cohort, it appears that there was a difference of almost 1 year of longer follow-up for the cytology period cohort than for the HPV period cohort. If so, then one cannot compare the two groups simply by number of cases of cervical cancer per 100,000 women years, since there would be a longer average time for cancer to have occurred in one group, thus they are not comparable rates. Also, the counts are so low that there is inadequate power from these data to extrapolate that there is no difference in cancer rates using the two screening methods. One can reasonably conclude that there is a difference rates of inadequate tests, rates of positive tests and colposcopies and that a higher proportion of (+) tests from HPV screening would result in
Fig 1: Should be in supplemental material, if at all. Should include number in each cohort at risk at the indicated times along the x axis. Legend should indicate the results of stats testing for the K-M plots.

EDITORIAL OFFICE COMMENTS:

1. The Editors of Obstetrics & Gynecology are seeking to increase transparency around its peer-review process, in line with efforts to do so in international biomedical peer review publishing. If your article is accepted, we will be posting this revision letter as supplemental digital content to the published article online. Additionally, unless you choose to opt out, we will also be including your point-by-point response to the revision letter. If you opt out of including your response, only the revision letter will be posted. Please reply to this letter with one of two responses:
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3. If you used an administrative database: In order for an administrative database study to be considered for publication in Obstetrics & Gynecology, the database used must be shown to be reliable and validated. In your response, please tell us who entered the data and how the accuracy of the database was validated. This same information should be included in the Materials and Methods section of the manuscript.

4. Responsible reporting of research studies, which includes a complete, transparent, accurate and timely account of what was done and what was found during a research study, is an integral part of good research and publication practice and not an optional extra. Obstetrics & Gynecology supports initiatives aimed at improving the reporting of health research, and we ask authors to follow specific guidelines for reporting randomized controlled trials (ie, CONSORT), observational studies (ie, STROBE), observational studies using ICD-10 data (ie, RECORD), meta-analyses and systematic reviews of

randomized controlled trials (ie, PRISMA), harms in systematic reviews (ie, PRISMA for harms), studies of diagnostic accuracy (ie, STARD), meta-analyses and systematic reviews of observational studies (ie, MOOSE), economic evaluations of health interventions (ie, CHEERS), quality improvement in health care studies (ie, SQUIRE 2.0), and studies reporting results of Internet e-surveys (CHERRIES). Include the appropriate checklist for your manuscript type upon submission. Please write or insert the page numbers where each item appears in the margin of the checklist. Further information and links to the checklists are available at http://ong.editorialmanager.com. In your cover letter, be sure to indicate that you have followed the CONSORT, MOOSE, PRISMA, PRISMA for harms, STARD, STROBE, RECORD, CHEERS, SQUIRE 2.0, or CHERRIES guidelines, as appropriate.

5. Standard obstetric and gynecology data definitions have been developed through the reVITALize initiative, which was convened by the American College of Obstetricians and Gynecologists and the members of the Women's Health Registry Alliance. Obstetrics & Gynecology has adopted the use of the reVITALize definitions. Please access the obstetric data definitions at https://www.acog.org/practice-management/health-it-and-clinical-informatics/revitalize-obstetrics-data-definitions and the gynecology data definitions at https://www.acog.org/practice-management/health-it-and-clinical-informatics/revitalize-gynecology-data-definitions. If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.

6. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Original Research reports should not exceed 22 typed, double-spaced pages (5,500 words). Stated page limits include all numbered pages in a manuscript (i.e., title page, précis, abstract, text, references, tables, boxes, figure legends, and print appendixes) but exclude references.

7. Specific rules govern the use of acknowledgments in the journal. Please note the following guidelines:

* All financial support of the study must be acknowledged.
* Any and all manuscript preparation assistance, including but not limited to topic development, data collection, analysis, writing, or editorial assistance, must be disclosed in the acknowledgments. Such acknowledgments must identify the entities that provided and paid for this assistance, whether directly or indirectly.
* All persons who contributed to the work reported in the manuscript, but not sufficiently to be authors, must be acknowledged. Written permission must be obtained from all individuals named in the acknowledgments, as readers may infer their endorsement of the data and conclusions. Please note that your response in the journal's electronic author form verifies that permission has been obtained from all named persons.
* If all or part of the paper was presented at the Annual Clinical and Scientific Meeting of the American College of Obstetricians and Gynecologists or at any other organizational meeting, that presentation should be noted (include the exact dates and location of the meeting).
* If your manuscript was uploaded to a preprint server prior to submitting your manuscript to Obstetrics & Gynecology, add the following statement to your title page: "Before submission to Obstetrics & Gynecology, this article was posted to a preprint server at: [URL]."

8. Provide a short title of no more than 45 characters (40 characters for case reports), including spaces, for use as a running foot.

9. The most common deficiency in revised manuscripts involves the abstract. Be sure there are no inconsistencies between the Abstract and the manuscript, and that the Abstract has a clear conclusion statement based on the results found in the paper. Make sure that the abstract does not contain information that does not appear in the body text. If you submit a revision, please check the abstract carefully.

In addition, the abstract length should follow journal guidelines. The word limit for Original Research articles is 300 words. Please provide a word count.

10. Only standard abbreviations and acronyms are allowed. A selected list is available online at http://edmgr.ovid.com/ong/accounts/abbreviations.pdf. Abbreviations and acronyms cannot be used in the title or précis. Abbreviations and

acronyms must be spelled out the first time they are used in the abstract and again in the body of the manuscript.

11. The journal does not use the virgule symbol (/) in sentences with words. Please rephrase your text to avoid using "and/or," or similar constructions throughout the text. You may retain this symbol if you are using it to express data or a measurement.

12. In your Abstract, manuscript Results sections, and tables, the preferred citation should be in terms of an effect size, such as odds ratio or relative risk or the mean difference of a variable between two groups, expressed with appropriate confidence intervals. When such syntax is used, the P value has only secondary importance and often can be omitted or noted as footnotes in a Table format. Putting the results in the form of an effect size makes the result of the statistical test more clinically relevant and gives better context than citing P values alone.

If appropriate, please include number needed to treat for benefits (NNTb) or harm (NNTh). When comparing two procedures, please express the outcome of the comparison in U.S. dollar amounts.

Please standardize the presentation of your data throughout the manuscript submission. For P values, do not exceed three decimal places (for example, "P = .001"). For percentages, do not exceed one decimal place (for example, 11.1%").

12. If your manuscript contains a priority claim: We discourage claims of first reports since they are often difficult to prove. How do you know this is the first report? If this is based on a systematic search of the literature, that search should be described in the text (search engine, search terms, date range of search, and languages encompassed by the search). If it is not based on a systematic search but only on your level of awareness, it is not a claim we permit.

13. Please review the journal's Table Checklist to make sure that your tables conform to journal style. The Table Checklist is available online here: http://edmgr.ovid.com/ong/accounts/table_checklist.pdf.

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In addition, the American College of Obstetricians and Gynecologists' (ACOG) documents are frequently updated. These documents may be withdrawn and replaced with newer, revised versions. If you cite ACOG documents in your manuscript, be sure the reference you are citing is still current and available. If the reference you are citing has been updated (ie, replaced by a newer version), please ensure that the new version supports whatever statement you are making in your manuscript and then update your reference list accordingly (exceptions could include manuscripts that address items of historical interest). If the reference you are citing has been withdrawn with no clear replacement, please contact the editorial office for assistance (obgyn@greenjournal.org). In most cases, if an ACOG document has been withdrawn, it should not be referenced in your manuscript (exceptions could include manuscripts that address items of historical interest). All ACOG documents (eg, Committee Opinions and Practice Bulletins) may be found at the Clinical Guidance page at https://www.acog.org/clinical (click on "Clinical Guidance" at the top).

15. Figure 1: Please upload as a figure file on Editorial Manager.

When you submit your revision, art saved in a digital format should accompany it. If your figure was created in Microsoft Word, Microsoft Excel, or Microsoft PowerPoint formats, please submit your original source file. Image files should not be copied and pasted into Microsoft Word or Microsoft PowerPoint.

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directly from the statistical program.

Figures should be saved as high-resolution TIFF files. The minimum requirements for resolution are 300 dpi for color or black and white photographs, and 600 dpi for images containing a photograph with text labeling or thin lines.

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If you choose to revise your manuscript, please submit your revision through Editorial Manager at http://ong.editorialmanager.com. Your manuscript should be uploaded in a word processing format such as Microsoft Word. Your revision's cover letter should include the following:

* A confirmation that you have read the Instructions for Authors (http://edmgr.ovid.com/ong/accounts/authors.pdf), and
* A point-by-point response to each of the received comments in this letter. Do not omit your responses to the Editorial Office or Editors' comments.

If you submit a revision, we will assume that it has been developed in consultation with your co-authors and that each author has given approval to the final form of the revision.

Again, your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Apr 23, 2021, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,
John O. Schorge, MD
Associate Editor, Gynecology

2019 IMPACT FACTOR: 5.524
2019 IMPACT FACTOR RANKING: 6th out of 82 ob/gyn journals

London and Copenhagen, 29 April 2021

Human papillomavirus testing in the last cervical screening round at age 60-64: Register-based study

RESPONSE LETTER

Jeppe Bennekou Schroll, Reza Rafiolsadat Serizawa, Matejka Rebolj

GENERAL RESPONSE:

We thank the editor and the reviewers for their insightful comments. We addressed them point by point as explained below. All changes in the text are tracked.

REVIEWER COMMENTS:

Reviewer #1:

Overall: Important topic, relevant to our current process change related to incorporating HPV for primary cervical cancer screening.
Abstract: clear and well written

Response: Thank you.

Introduction: Generally some grammatical and flow issues that I would recommend editing. Otherwise content is appropriate. The aims could be more completely stated, a bit vague as written.

Response: We were unsure which Introduction this comment referred to and have edited the text in both the Abstract and in the main text. The sections on the objectives of the study were rephrased as follows:

> ***Abstract:***
> ***Objective.*** *The evidence on using high-risk human papillomavirus (HPV) testing in cervical cancer screening in older women is limited. In 2012, the Danish cervical cancer screening program replaced cytology with HPV testing as the primary screening method for women between the ages of 60 and 64, who are in their last recommended screening round before exiting the program. Using data routinely collected in the national pathology register, our aim was to compare the real-life screening outcomes after cytology was replaced by HPV testing for women aged 60-64 years.*
>
> ***Main text:***
> *Our aim was to report the outcomes of the first four years of routinely implemented HPV-based screening at ages 60-64 in Denmark, in comparison with cytology. We studied the proportions of women with inadequate and positive screening tests, with detected high-grade CIN, and a cervical cancer diagnosis.*

Methods:
* The first paragraph is very confusing. This description might work well if the reader was more knowledgeable about the system in Denmark, but I am uncertain what a "personal invitation" is. By mail? Electronically?

Response: We apologize that the text was confusing. In response, we rephrased the paragraph as follows:

In Denmark, organized (call/recall) cervical screening started on a regional basis in the 1960's and became national in the second half of the 1990's. Personal invitations are sent electronically or by letter to all resident women who fulfil the age eligibility and screening history criteria for the program (see below), are not registered as having had a hysterectomy, and did not actively opt out of the program. These invitations play a role of a safety net for women who do not obtain regular screening on their own accord i.e., when they do not have a screening sample registered in the national pathology database, Patobank, in the last three years (if aged 23-49) or in the last five years (if aged 50-64). Screening samples of women that were taken without an invitation are usually referred to as "opportunistic", although they equally contribute to the national screening coverage as do samples taken after an invitation.[10]

* Also, Lines 102-105 don't seem appropriate for the methods section.

Response: The information reported therein, on the proportion of women screened, reports background information which we believe is useful in interpreting the results of the study. It confirms that by far the majority of the women targeted by the program participated in screening. This information could not be independently reported as part of the Results, as we did not have access to all relevant registers. To emphasize this, we have now rephrased the section as follows:

Most women in the target population participate in screening, as the age-appropriate coverage has been around 73% in the recent years.[11] *Corrected for hysterectomies, furthermore, the 5.5-year coverage in women aged 60-64 was estimated at around 77% in 2010.*[12] *Historical data for birth cohorts included in our analysis suggest that the majority of women included in the present analysis must have participated in screening throughout their entire lives.*[6]

* I don't know what "well-screened" means - should be defined.

Response: We rephrased the sentence; please refer to the previous comment ("*must have participated in screening throughout their entire lives*").

* There is considerable variation between regions, which is somewhat confusion.

Response: Indeed, there has been some variation between the regions in terms of which brands of tests were used and in the triage process for women with positive screens. This variability is not unusual for a routine implementation of cervical screening. We reported the following under Strengths and Limitations, in the original submission: "*While cytology was the recommended primary screening test, laboratories used both conventional and liquid-based technologies; during the HPV period, all laboratories used liquid-based technologies but different HPV assays. Hence, the analyses should be understood as comparing routine implementation of two distinct types of screening tests rather than a comparison of specific testing technologies or even brands.*" Furthermore, the widely acclaimed meta-analysis of four randomized trials comparing HPV testing with cytology (Ronco et al., Lancet 2014) noted that while the trials employed different triage protocols, this did not affect the effectiveness of HPV-based screening. In our paper, we noted (Results/para 3) that all regions achieved a higher CIN2+ detection rate with HPV testing than was the case with cytology.

* When noted "discharged for the program" was that anyone between 60-64?

Response: Yes indeed, as reported in the Introduction, women are "*discharged from the program on account of their age*." No new screening invitations will be issued to them after a negative test in that round, or after resolution of a screen-detected abnormality.

* The paragraph between lines 155-172 is extremely confusing. This paragraph needs to be reworked, or broken into several paragraphs to make the content clearer.

Response: We apologise for this. The paragraph is now rephrased as follows:

> *We included the first primary screening sample for each woman if it was taken at age 60-64 years between 1 January 2009 and 31 December 2016. Age was determined from the woman's date of birth and the date the sample arrived in a laboratory.*
>
> *As the reason for taking a sample is not reliably registered in the Patobank, we defined a primary screening sample as cervical cytology or HPV testing that was not preceded by another cervical testing record in the Patobank in two years. In line with the definitions used for the national program monitoring scheme undertaken by the Danish Quality Database for Cervical Screening,[11] we additionally excluded samples that were described as consultation material, marked for various types of special (non-standard) testing, or taken for research purposes.*
>
> *We compared all primary screening samples during the HPV screening period to those during the cytology screening period. During the HPV screening period (Table 1), we included women who were still being screened with cytology. This is because in both observed periods, women who chose to be screened without receiving an invitation may have had a different risk profile than women who waited for their invitation and excluding them from the analysis could introduce bias. As each regional laboratory switched from cytology to HPV testing at different times between February 2012 and August 2014 (Table 1), we defined periods of screening with cytology and periods of screening with HPV testing depending on the region. In regions with several screening laboratories, the end of the cytology period was defined as the date the first of the laboratories switched to HPV testing, while the beginning of the HPV period was defined as the date the last of the laboratories switched to HPV testing. Samples were assigned to a particular region based on the laboratory code.*
>
> *Owing to data protection restrictions, we could not report exact counts when those were lower than or equal to five.*

Results: Clear and well written

Discussion:

* Lines 258-271: Some component of this should be outlined in the methodology.

Response: We have moved parts of that paragraph to Methods as follows:

> ***Methods (previously in part in Discussion):***
> *We classified SNOMED codes for squamous and glandular lesions into diagnostic categories based on previous work.[15] One of the authors (RRS) checked this categorisation and added any recently introduced codes.*
>
> *The pathology register reflects the daily production in routine pathology laboratories, and so histology SNOMED strings sometimes include inconclusive malignancy codes. Consequently, the numbers of apparent cases of cervical cancer reported in this register tend to overestimate the numbers from the official national cancer statistics. For our study, a pathologist who reports to the pathology register on a daily basis (RRS) and a gynaecologist who is a daily pathology register user (JBS) corrected the counts using the information*

available in the SNOMED string for each case. The record was counted as a diagnosis of cervical cancer if the string suggested that cervix uteri was the primary location.

* Lines 273-277: Should be incorporated elsewhere, does not stand alone.
* Overall, the discussion is very verbose and a bit jumbled. It was hard to follow.
* There is a comprehensive discussion of the limitations, but I think these could be consolidated and presented in a more concise manner. Perhaps some of the background information could be better incorporated into the introduction.

Response: These three points are related and were handled jointly. We apologise that the Discussion was hard to follow. We have now revised it thoroughly, consolidated the different points in more concise paragraphs, and shortened the text by about 700 words.

Reviewer #2:

This is large population based observational study to evaluate the outcomes of adding HPV testing to the "exist" screening visit for cervical cancer in women 60-64 years compared to other methods of screening
Main issues:
1- The heterogeneity of the different protocol and the small number of outcomes which is expected are important factors that affect the reliability of this study as well as other studies evaluating cervical cancer screen. Still, this is a large database that is population based. How did the authors account for this heterogeneity and how much did this affect the results?

Response: Reviewer #1 asked the same question on the heterogeneity between the regions; please see our response above. For reasons stated in our response, we do not believe that the variability of the protocols affected the reliability of our study.

Another comment made by several reviewers relates to the small number of certain outcomes. We need to emphasize that our study was not a clinical trial designed to test a hypothesis. Rather, it was an observational study describing the outcomes of two alternative screening technologies used in routine clinical practice. Here, the small number of outcomes such as cancers after a negative screen is informative and is a testament to the high effectiveness of the screening methods. The study included all women who underwent cervical screening in the entire country, using data allowing for a virtually complete enumeration of the studied outcomes regardless of the screening provider, region, health insurance, and similar factors. This study and the numbers of outcomes are representative of the entire population.

2- For the number of positive testing and CIN2 and CIN3, did the author adjust for known risk factors?

Response: Unfortunately, our study did not have access to information on sociodemographic characteristics of the women. However, Denmark is a rather homogeneous country and there were no known social changes during the study period which could meaningfully affect the comparisons made in the analysis. We described this as follows in the Discussion, in the original submission: "*We did not have data available for analysis with which to adjust for any sociodemographic differences between women screened during those two periods. However, these factors[16] were likely unchanged between the two periods, judging by how constant screening coverage has been over time and between regions.[17 18] It is also unlikely that the underlying risk of cervical cancer*

differed between the two cohorts, given the short periods for inclusion of samples in the two chronologically adjacent periods."

Specific issues:

1- Methods:

a. Did the authors consider any sample size estimation and what is the primary outcome of this study? Please include the primary outcome

Response: As explained above, this was an observational study designed to describe screening outcomes rather than test a hypothesis. From the outset, we relied on the inclusion of all women screened at 60-64 years of age in the entire country. Even if we considered an a priori sample size estimation, this would not affect the study's design as we were limited by the size of the Danish population (currently: about 5.84 million).

Our primary study outcomes are now defined in the Introduction as "*the proportions of women with inadequate and positive screening tests, with detected high-grade CIN, and a cervical cancer diagnosis*". This information is repeated in Methods, with additional detail.

b. Did the author considered regression analysis to adjust for known risk factors?

Response: No, we could unfortunately not do that; please see the response to "Main issues"/2 above.

c. Did the author consider CIN2 and CIN3 as the outcome of study rather than cervical cancer and did they adjust for known risk factors? Did the author use proportional hazard modeling to adjust for potential confounders?

Response: Both CIN2/3 and cervical cancer were equally important as screening outcomes in our study. Please see above on adjustment for confounders.

2- Results:

a. What was the follow up duration and is it different between the 2 groups, please add to table 2. Did the author limit the follow up to certain time in both groups?

Response: In Table 2, we reported detection of abnormalities at screening. These abnormalities were detected within 2 years of screening, as explained in Methods. All women had at least 2 years of follow-up available in our data.

b. Please add another figure with CIN2 and CIN3 as the primary outcome for a survival analysis.

Response: CIN2 and CIN3, but also screen-detected cervical cancer, are asymptomatic diagnoses made in women with positive screens around the time that clinical management guidelines recommend the follow-up to take place. In Denmark, the majority of these lesions are diagnosed within weeks after the primary screen, or within weeks after the 12-month repeat test, if the woman is referred to it. Detection outside of those timeframes is low. The cumulative detection function in a survival analysis would, therefore, have two bumps after the baseline and after the repeat test with little else going on. In contrast, please note that the reason we chose to report a survival curve for the incidence of cancer after a negative screen is that those cancers are typically diagnosed following symptoms, at intervals that are more aligned with the aetiology of the disease (i.e., the gradual surfacing of symptoms).

c. To address heterogeneityKM, using a multivariate proportional hazard model might help

Response: Please see our response on adjustment for confounders above.

3- Discussion:
a. Can be shorter

Response: We have now thoroughly revised the entire Discussion and shortened it by about 700 words.

b. Please compare the incidence of CIN2 and 3 in this study with the prior 4 RCTS that did not detect a difference in the cervical cancer detection rate.

Response: The four RCTs are not easily comparable with the way screening was carried out in this study. In the four RCTs, women of all screening ages, <30 to >60, were represented. Cytology was read without knowledge of the HPV test outcome. In our study of routine implementation of HPV testing, cytopathologists knew that the woman was HPV positive (as explained in the text), which may have increased the proportion with a positive triage result. Furthermore, referrals to colposcopy were prioritised for women with HPV16/18 infections, which was not the case in the trials. In the trials, follow-up after a positive HPV screening test with negative triage cytology was low, between 50 and 70% (Rebolj and Lynge, BJC 2010), which may also explain why some of the cancers were not detected early.

Reviewer #3:

This study is a retrospective analysis of the implementation of
primary HPV screening compared with previous cytology based cervical cancer screening in the age group of woman exiting from screening. Methods and outcomes are well described. Impacts of HPV testing on screen positive rates, detection of high grade dysplasia and cancers and number of colposcopies and potential surgical procedures are well described. This paper highlights many of the issues of primary HPV testing in this age group and the challenges of when and how to exit cervical cancer screening. Some of this paper's findings have previously been published but in smaller numbers of women. What is unique to this paper is the large number of women from a population database. As the appropriate age to stop cervical cancer screening is unclear it is important to have papers like this, which document advantages and disadvantages of different exit screening tests. The short term follow up of significant disease is also informative but longer term data is needed.

Response: Thank you.

How did your study distinguish when labs were doing primary HPV testing verses primary cytology with HPV triage? Was it based on particular HPV assay? For example in Table 1 the Capital region was using Hybrid capture until Oct 2014 yet HPV period analysis started August 2014 - was the hybrid capture2 test used for primary HPV testing? As hybrid capture 2 is usually used for reflex/triage or contesting and not primary HPV testing?

Response: The information on when the laboratories used HPV testing vs cytology as the primary screening test was obtained directly from the laboratories, from the individuals identified in the Acknowledgments. These persons also reported which screening technology brand was used, and when. Indeed, the Capital Region used HC2 for primary screening, similarly as some of the four randomized trials mentioned above. The reason

for a change in the HPV testing system in this Region was unrelated to the implementation of HPV-based primary screening at the age of 60-64.

Did individual labs have times during transition where they were doing both primary HPV and cytology screening or did they abruptly transition and do only primary HPV testing with cytology triage and no more cytology screening? You describe that happening with opportunistic verses invited screening tests but it was unclear if there was an overlap period even for invited tests. Did any of the labs ever do cotesting?

Response: No, none of the Danish laboratories did co-testing i.e., both cytology and HPV testing as a combined primary screening method on the same screening sample. Co-testing was never recommended by the national screening guidelines. The laboratories did indeed relatively abruptly transition from one to the other screening test, but the technology and the know-how had already been available in the laboratories e.g., for the purpose of HPV triage of ASCUS/LSIL primary screens. The transition was further progressed by the fact that various administrative decisions and the national clinical management guidelines for women with positive screens had been agreed well in advance.

In the patients with screen negative testing and subsequent cervical cancer diagnosis could their previous screening histories prior to age 60 be reported? It would be useful to know if they had been well screened up to that point and if they had any abnormal cytology in the decade before they were to exit screening.
Line 165 defined primary screening - if no cervical record prior 2 years. Is it possible some woman with recently detected HSIL or treated high grade CIN might miss a year or two of follow up? Could your database be queried for CIN diagnosed in the past decade and possibly analyze these women differently than the "low" risk women who should be exiting screening?

Response: We joined these two questions, as they require the same answer. We agree that this would be interesting to study. Unfortunately, data on women's screening histories were not available for this project. To get hold of this information would require a different approval for data retrieval.

Table 2. Why were the 17% with cytology from opportunistic tests included in HPV period? It would be best to also report the analysis with these results removed.

Response: We added an explanation as follows (in Methods):

> *We compared all primary screening samples during the HPV screening period to those during the cytology screening period. During the HPV screening period (Table 1), we included women who were still being screened with cytology. This is because in both observed periods, women who chose to be screened without receiving an invitation may have had a different risk profile than women who waited for their invitation and excluding them from the analysis could introduce bias.*

Line 358 - "substituting cytology for HPV"- this seems confusing as you are substituting HPV for cytology.

Response: We apologise. We have rephrased this as follows:

> *Replacing cytology with HPV testing in women in their early sixties, most of whom are postmenopausal, will have an important effect on screening services such as primary care, pathology, and colposcopy.*

There are several studies from Sweden that look at women 60 years and older having primary HPV, with some comparison to cytology screening. These studies are relevant to your study and should be discussed.

Response: Sweden does not recommend population-based cervical screening to women older than 60. Therefore, the recent publications such as that by Sahlgren et al. Am J Obstet Gynecol 2020, refer to women below the age of 60 at their last recommended screening test. This is a younger age than in Denmark and women had had (at least) one fewer round of screening. That study was much smaller than ours; it included e.g., 405 HPV-positive women compared to 2891 in our study and reported no detected cancers. Other studies e.g., Hermansson et al. PLOS One 2018, included women older than 60 but it appears that women were sampled from among those who were seeking gynecological care for other reasons so do not represent a typical screening population.

STATISTICS EDITOR COMMENTS:

Abstract: Should include the number of women and women-years in each cohort. See later comments re: The risk rate cited.

Response: This is now included as follows:

> *Within the first four years after a negative screening test, including 168,477 woman-years at risk after a negative screen in the HPV period and 451,421 woman-years after a negative screen in the cytology period, the risk of a cervical cancer diagnosis was around 4 per 100,000 woman-years and was similar for both screening tests (relative risk: 0.99, 95% CI: 0.41-2.35).*

Table 2: While this Table is informative, should also include a flow diagram following the explanation for the two cohorts as on lines 198-204. For the HPV period cohort, begin with 54397, subtract 343 as inadequate test, then have 54054 remaining. Of those, 2891 had (+) screen, of those 2739 (94.7%) had follow-up, of those, 1770 (64.6%) had colposcopy, of those, 1503 (84.9%) had < CIN2, 267 (15.1% had CIN2+ etc. Then show corresponding counts and % for the cytology period cohort. I think that this would make the proportions less confusing for the reader.

Response: We have now added the flowchart as Figure 1.

lines 226-230: Using the data provided, I obtained a slightly
different RR 0.99 (95% CI 0.42-2.35). Please verify your calculations. Also, given the number of patients and the counts for women-years in each cohort, it appears that there was a difference of almost 1 year of longer follow-up for the cytology period cohort than for the HPV period cohort. If so, then one cannot compare the two groups simply by number of cases of cervical cancer per 100,000 women years, since there would be a longer average time for cancer to have occurred in one group, thus they are not comparable rates. Also, the counts are so low that there is inadequate power from these data to extrapolate that there is no difference in cancer rates using the two screening methods. One can reasonably conclude that there is a difference rates of inadequate tests, rates of positive tests and colposcopies and that a higher proportion of (+) tests from HPV screening would result in <CIN2 cytology, but not that cervical cancer rates are equivalent.
Fig 1: Should be in supplemental material, if at all. Should include number in each cohort at risk at the indicated times along the x axis. Legend should indicate the results of stats testing for the K-M plots.

Response: We merged the response to these points, as we believe that they address related issues. We have verified our calculations and, other than rounding (now rectified), could not identify any issues with the counting of woman-years. The difference in the RR, we believe, is due to the different method used by the statistical package; we have now changed it so that the estimates align better with yours. This required the change in the Abstract (as reported above), in Methods, and in Results:

> ***Methods:***
> *The 95% CI for a relative risk was calculated by using Wald's normal approximation, with help from the 'epitools' package in R version 4.02.*
>
> ***Results:***
> *The relative risk for the HPV period compared to the cytology period was 0.99 (95% CI: 0.41-2.35), based on seven cases in the HPV period (168,477 woman-years at risk) and 19 cases in the cytology period (451,421 woman-years at risk, Figure 2).*

Please see above for our detailed response on the low number of cases in this part of the analysis. In short, this study included all women undergoing screening in Denmark and all cases that accrued in them in several years. By the end of 4 years of follow-up, there were still more than 20,000 women screened with HPV testing that remained under observation, which is not a low number particularly when a very narrow age group is concerned. For comparison, all 4 randomized trials combined included 94,000 women screened with HPV testing at any age (below 30 to above 60). The low risk, we believe, is important to describe in the literature, as it attests to the high quality of screening with either method. We did not attempt to do any hypothesis testing, but we simply stated that within the first 4 years the residual risks were much the same regardless of the screening test ("*In the first four years after screening with a negative test, the risk of cervical cancer remained low.*" And later: "*In this initial phase of a national implementation of HPV testing in the "exit" round, the data do not yet show a decrease in the incidence of cervical cancer after a negative screening test compared to cytology-based screening.*").

We chose to censor follow-up after a negative screen at 4 years because women screened in the HPV period had up to 6.5 years of follow-up available in our data. After this censoring, we ended up with about 3.3 years on average for women screened in the HPV period and almost 4.0 years for women screened in the cytology period. We agree that a difference in the average follow-up times could affect the calculated RR, and we were aware of this when writing up the paper. The KM curve, however, reassured us that this could not have affected our conclusion of no major difference in the risk between the two screening methods (the curves are very close to one another during the entire follow-up).

We edited the KM curve as requested: we added the numbers at risk along the x-axis and the log-rank p-value.

EDITORIAL OFFICE COMMENTS:

1. The Editors of Obstetrics & Gynecology are seeking to increase transparency around its peer-review process, in line with efforts to do so in international biomedical peer review publishing. If your article is accepted, we will be posting this revision letter as supplemental digital content to the published article online. Additionally, unless you choose to opt out, we will also be including your point-by-point response to the revision letter. If you opt out of including your response, only the revision letter will be posted. Please reply to this letter with one of two responses:
A. OPT-IN: Yes, please publish my point-by-point response letter.

B. OPT-OUT: No, please do not publish my point-by-point response letter.

Response: Opt-in, please.

2. Obstetrics & Gynecology uses an "electronic Copyright Transfer Agreement" (eCTA). Please check with your coauthors to confirm that the disclosures listed in their eCTA forms are correctly disclosed on the manuscript's title page. Each of your coauthors received an email from the system, titled "Please verify your authorship for a submission to Obstetrics & Gynecology." Each author should complete the eCTA if they have no yet done so.

Response: We believe we have all completed the eCTA following the link in the email you sent us. If anything went wrong, we would appreciate if you could email us the link one more time.

3. If you used an administrative database: In order for an administrative database study to be considered for publication in Obstetrics & Gynecology, the database used must be shown to be reliable and validated. In your response, please tell us who entered the data and how the accuracy of the database was validated. This same information should be included in the Materials and Methods section of the manuscript.

Response: The Danish national pathology database, which was the data source for our analysis, is a real-time register that all laboratories report to electronically. The processes and the data validation have been described in detail in reference 13 (this reference replaced the previous reference #13).

4. Responsible reporting of research studies, which includes a complete, transparent, accurate and timely account of what was done and what was found during a research study, is an integral part of good research and publication practice and not an optional extra. Obstetrics & Gynecology supports initiatives aimed at improving the reporting of health research, and we ask authors to follow specific guidelines for reporting randomized controlled trials (ie, CONSORT), observational studies (ie, STROBE), observational studies using ICD-10 data (ie, RECORD), meta-analyses and systematic reviews of randomized controlled trials (ie, PRISMA), harms in systematic reviews (ie, PRISMA for harms), studies of diagnostic accuracy (ie, STARD), meta-analyses and systematic reviews of observational studies (ie, MOOSE), economic evaluations of health interventions (ie, CHEERS), quality improvement in health care studies (ie, SQUIRE 2.0), and studies reporting results of Internet e-surveys (CHERRIES). Include the appropriate checklist for your manuscript type upon submission. Please write or insert the page numbers where each item appears in the margin of the checklist. Further information and links to the checklists are available at https://eur03.safelinks.protection.outlook.com/?url=http%3A%2F%2Fong.editorialmanager.com%2F&data=04%7C01%7Cmatejka.rebolj%40kcl.ac.uk%7Ce6c42f47c51e4df14be408d8f6a85c9d%7C8370cf1416f34c16b83c724071654356%7C0%7C0%7C637530550265154101%7CUnknown%7CTWFpbGZsb3d8eyJWIjoiMC4wLjAwMDAiLCJQIjoiV2luMzIiLCJBTiI6Ik1haWwiLCJXVCI6Mn0%3D%7C1000&sdata=D4AqDvfKzyFe%2B%2FiOQ%2FGstvJsUA%2BFVIOgUaTZBP1pVgI%3D&reserved=0. In your cover letter, be sure to indicate that you have followed the CONSORT, MOOSE, PRISMA, PRISMA for harms, STARD, STROBE, RECORD, CHEERS, SQUIRE 2.0, or CHERRIES guidelines, as appropriate.

Response: We have followed the STROBE reporting guidelines for observational studies, and the completed form was submitted to the journal.

5. Standard obstetric and gynecology data definitions have been developed through the reVITALize initiative, which was convened by the American College of Obstetricians and Gynecologists and the members of the Women's Health Registry Alliance. Obstetrics & Gynecology has adopted the use of the reVITALize definitions. Please access the obstetric data definitions at https://eur03.safelinks.protection.outlook.com/?url=https%3A%2F%2Fwww.acog.org%2Fpractice-management%2Fhealth-it-and-clinical-informatics%2Frevitalize-obstetrics-data-definitions&data=04%7C01%7Cmatejka.rebolj%40kcl.ac.uk%7Ce6c42f47c51e4df14be408d8f6a85c9d%7C8370cf1416f34c16b83c724071654356%7C0%7C0%7C637530550265154101%7CUnknown%7CTWFpbGZsb3d8eyJWIjoiMC4wLjAwMDAiLCJQIjoiV2luMzIiLCJBTiI6Ik1haWwiLCJXVCI6Mn0%3D%7C1000&sdata=PLegA6W%2BNM%2Fwp3PUMYATH8DfF92NCVvfgVHRIQWv5xA%3D&reserved=0 and the gynecology data definitions at https://eur03.safelinks.protection.outlook.com/?url=https%3A%2F%2Fwww.acog.org%2Fpractice-management%2Fhealth-it-and-clinical-informatics%2Frevitalize-gynecology-data-definitions&data=04%7C01%7Cmatejka.rebolj%40kcl.ac.uk%7Ce6c42f47c51e4df14be408d8f6a85c9d%7C8370cf1416f34c16b83c724071654356%7C0%7C0%7C637530550265154101%7CUnknown%7CTWFpbGZsb3d8eyJWIjoiMC4wLjAwMDAiLCJQIjoiV2luMzIiLCJBTiI6Ik1haWwiLCJXVCI6Mn0%3D%7C1000&sdata=JdIBUANlQtxpYlNAkLbRuFfkkc4MyWFLhPiUl3qtHHA%3D&reserved=0. If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.

Response: We now spell ASCUS as ASC-US in the revised version. We believe that we used other terminology as recommended by reVITALize.

6. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Original Research reports should not exceed 22 typed, double-spaced pages (5,500 words). Stated page limits include all numbered pages in a manuscript (i.e., title page, précis, abstract, text, references, tables, boxes, figure legends, and print appendixes) but exclude references.

Response: Following revisions, we have substantially shortened the text, which now includes 3758 words.

7. Specific rules govern the use of acknowledgments in the journal. Please note the following guidelines:

* All financial support of the study must be acknowledged.

Response: All financial support was acknowledged.

* Any and all manuscript preparation assistance, including but not limited to topic development, data collection, analysis, writing, or editorial assistance, must be disclosed in the acknowledgments. Such acknowledgments must identify the entities that provided and paid for this assistance, whether directly or indirectly.

Response: We received no manuscript preparation assistance; the manuscript is the result of the work of the three co-authors.

* All persons who contributed to the work reported in the manuscript, but not sufficiently to be authors, must be acknowledged. Written permission must be obtained from all individuals named in the acknowledgments, as readers may infer their endorsement of the data and conclusions. Please note that your response in the journal's electronic author form verifies that permission has been obtained from all named persons.

Response: We have received a permission by email from all persons listed in Acknowledgments.

* If all or part of the paper was presented at the Annual Clinical and Scientific Meeting of the American College of Obstetricians and Gynecologists or at any other organizational meeting, that presentation should be noted (include the exact dates and location of the meeting).

Response: A preliminary version of the results from this study was presented at Eurogin 2019. We have noted this in the paper.

* If your manuscript was uploaded to a preprint server prior to submitting your manuscript to Obstetrics & Gynecology, add the following statement to your title page: "Before submission to Obstetrics & Gynecology, this article was posted to a preprint server at: [URL]."

Response: This paper was not uploaded to a preprint server.

8. Provide a short title of no more than 45 characters (40 characters for case reports), including spaces, for use as a running foot.

Response: We have added a running foot ("*HPV testing in the last screening round*").

9. The most common deficiency in revised manuscripts involves the abstract. Be sure there are no inconsistencies between the Abstract and the manuscript, and that the Abstract has a clear conclusion statement based on the results found in the paper. Make sure that the abstract does not contain information that does not appear in the body text. If you submit a revision, please check the abstract carefully.

In addition, the abstract length should follow journal guidelines. The word limit for Original Research articles is 300 words. Please provide a word count.

Response: We have checked the consistency between the abstract and the main text and believe that the abstract is an honest representation of the findings described in the main text. The word count for the abstract is 289.

10. Only standard abbreviations and acronyms are allowed. A selected list is available online at https://eur03.safelinks.protection.outlook.com/?url=http%3A%2F%2Fedmgr.ovid.com%2Fong%2Faccounts%2Fabbreviations.pdf&data=04%7C01%7Cmatejka.rebolj%40kcl.ac.uk%7Ce6c42f47c51e4df14be408d8f6a85c9d%7C8370cf1416f34c16b83c724071654356%7C0%7C0%7C637530550265154101%7CUnknown%7CTWFpbGZsb3d8eyJWIjoiMC4wLjAwMDAiLCJQIjoiV2luMzIiLCJBTiI6Ik1haWwiLCJXVCI6Mn0%3D%7C1000&sdata=eIh3OJJYy37M9ctNm2zQps%2BGa3AT8ohgP7nlPbqjwmo%3D&reserved=0. Abbreviations and acronyms cannot be used in the title or précis. Abbreviations and acronyms must be spelled out the first time they are used in the abstract and again in the body of the manuscript.

Response: We did not use abbreviations and acronyms in the title or precis. While certain abbreviations that we used in our text, such as CIN, PPV, or SNOMED, do not appear in the list provided above, they are spelled out the first time they were used, and we believe they should also be familiar to readers with an interest in cancer screening.

11. The journal does not use the virgule symbol (/) in sentences with words. Please rephrase your text to avoid using "and/or," or similar constructions throughout the text. You may retain this symbol if you are using it to express data or a measurement.

Response: We have now replaced the virgule symbol throughout the main text.

12. In your Abstract, manuscript Results sections, and tables, the preferred citation should be in terms of an effect size, such as odds ratio or relative risk or the mean difference of a variable between two groups, expressed with appropriate confidence intervals. When such syntax is used, the P value has only secondary importance and often can be omitted or noted as footnotes in a Table format. Putting the results in the form of an effect size makes the result of the statistical test more clinically relevant and gives better context than citing P values alone.

If appropriate, please include number needed to treat for benefits (NNTb) or harm (NNTh). When comparing two procedures, please express the outcome of the comparison in U.S. dollar amounts.

Please standardize the presentation of your data throughout the manuscript submission. For P values, do not exceed three decimal places (for example, "P = .001"). For percentages, do not exceed one decimal place (for example, 11.1%").

Response: In the Abstract, all results were cited as relative risks and relative proportions. Throughout the text, all results reported as percentages are given with one decimal place.

12. If your manuscript contains a priority claim: We discourage claims of first reports since they are often difficult to prove. How do you know this is the first report? If this is based on a systematic search of the literature, that search should be described in the text (search engine, search terms, date range of search, and languages encompassed by the search). If it is not based on a systematic search but only on your level of awareness, it is not a claim we permit.

Response: Our manuscript does not include a priority claim.

13. Please review the journal's Table Checklist to make sure that your tables conform to journal style. The Table Checklist is available online here: https://eur03.safelinks.protection.outlook.com/?url=http%3A%2F%2Fedmgr.ovid.com%2Fong%2Faccounts%2Ftable_checklist.pdf&data=04%7C01%7Cmatejka.rebolj%40kcl.ac.uk%7Ce6c42f47c51e4df14be408d8f6a85c9d%7C8370cf1416f34c16b83c724071654356%7C0%7C0%7C637530550265154101%7CUnknown%7CTWFpbGZsb3d8eyJWIjoiMC4wLjAwMDAiLCJQIjoiV2luMzIiLCJBTiI6Ik1haWwiLCJXVCI6Mn0%3D%7C1000&sdata=DNRBMeH8%2BR66U2Gi3Yw5N9TtGRBWU5FL7tEQz0FfrCc%3D&reserved=0.

Response: We have now formatted the tables as per the journal's guidance.

14. Please review examples of our current reference style at https://eur03.safelinks.protection.outlook.com/?url=http%3A%2F%2Fong.editorialmanager.com%2F&data=04%7C01%7Cmatejka.rebolj%40kcl.ac.uk%7Ce6c42f47c51e4df14be408d8f6a85c9d%7C8370cf1416f34c16b83c724071654356%7C0%7C0%7C637530550265154101%7CUnknown%7CTWFpbGZsb3d8eyJWIjoiMC4wLjAwMDAiLCJQIjoiV2luMzIiLCJBTiI6Ik1haWwiLCJXVCI6Mn0%3D%7C1000&sdata=D4AqDvfKzyFe%2B%2FiOQ%2FGstvJsUA%2BFVIOgUaTZBP1pVgI%3D&reserved=0 (click on the Home button in the Menu bar and then "Reference Formatting Instructions" document under "Files and Resources). Include the digital object identifier (DOI) with any journal article references and an accessed date with website references. Unpublished data, in-press items, personal communications, letters to the editor, theses, package

inserts, submissions, meeting presentations, and abstracts may be included in the text but not in the reference list.

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Response: We have reformatted the reference list so that it now follows the journal's guidance.

15. Figure 1: Please upload as a figure file on Editorial Manager.

When you submit your revision, art saved in a digital format should accompany it. If your figure was created in Microsoft Word, Microsoft Excel, or Microsoft PowerPoint formats, please submit your original source file. Image files should not be copied and pasted into Microsoft Word or Microsoft PowerPoint.

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Figures should be saved as high-resolution TIFF files. The minimum requirements for resolution are 300 dpi for color or black and white photographs, and 600 dpi for images containing a photograph with text labeling or thin lines.

Art that is low resolution, digitized, adapted from slides, or downloaded from the Internet may not reproduce.

Response: We have followed the journal's guidelines to format figures, and hope that they will pass the checks.

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