Dear Miss Luijken,

Thank you for sending us this paper. I’m sorry it has taken longer than usual to write to you. I have recently been ill with COVID-19 despite double vaccination and this has delayed my correspondence.

We were pleased to have the chance to consider your work. We sent it out for external peer review and discussed it at the manuscript committee meeting. After careful consideration, we decided not to publish it in The BMJ in its present form. Our reasons are explained below in the report from the manuscript meeting.

However if you are able to amend it in the light of our and the reviewer comments, we would be happy to consider it again. Please note that resubmitting your manuscript does not guarantee eventual acceptance, and that your resubmission may be sent again for review.

The reviewer reports are available at the end of this letter.

Although The BMJ has an open peer review process, in which authors know who the peer reviewers were, we expect that you will keep the identity and comments of the peer reviewers for this paper confidential. You may, however, share the peer review comments in confidence (though not the names of the peer reviewers) with other journals to which you submit the paper. If you have any complaints about the peer review process or the conduct of the peer reviewers, please contact the editor who handled your paper. Please do not contact the peer reviewers directly.

Best wishes,

Dr John Fletcher
Associate Editor
The BMJ
jfletcher@bmj.com

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Report from The BMJ’s manuscript meeting:

At the manuscript meeting the editor makes the final decisions on accepting original papers submitted to the journal. At the manuscript meeting each article is discussed by The BMJ’s international team of research editors and one statistician. When making decisions we take into account each paper’s originality, scientific merits, and interest to a general readership in comparison with other submitted papers. We take reviewer reports fully into account too, but the final decision on acceptance or rejection of a paper rests with the editors.

These comments are an attempt to summarise the discussions at the manuscript meeting. They are not an exact transcript.

Members of the committee were: Elizabeth Loder (chair); Julie Morris (statistician); Tiago Villanueva; Wim Weber; Di Wang; Nazrul Islam; Navjoyt Ladher; John Fletcher.

Decision: rejection and offer
Detailed comments from the meeting:

1. We all warmed to the topic of how to avoid being mislead by exploratory analyses and the need to exercise caution in interpretation but we don't find that this article fits well with the aims of the Research Methods and Reporting section.

2. We prefer articles that give firm practical guidance for how to carry out a method or report a study design. Here the guidance would probably be how to report exploratory analyses.

3. When we publish reporting guidelines we like to be reassured that the guidance is authoritative and likely to be followed. This may stem from a process involving experts, a wide range of stakeholders and a consensus process. Sometimes, though less frequently, the authority stems from the authors and the quality of the writing itself.

4. Some real examples earlier on in the manuscript would help illustrate what you are discussing.

5. We were not convinced of the continuum you describe.

6. Perhaps you could give an indication of the scale and seriousness of the problem (e.g. how much of a part does it play in research waste? Could one argue that it helps lessen research waste if it is leading to less salami slicing of papers?)

7. Please view the comments of the independent reviewers which are included at the end of this email.

Reviewer: 1

Recommendation:

Comments:
This interesting paper addresses an important topic that I imagine would be useful to many BMJ readers. I have the following major and minor concerns:

Major

The number of exploratory or confirmatory analyses that can be rigorously conducted with a single dataset is the subject of ongoing debate to the extent that there is not agreement about if or when p-values, SEs or CIs should be adjusted for multiple testing. For this reason, a growing number of scientists calling for elimination of statistical tests and p-values altogether to address the reproducibility crisis (e.g. see https://journals.lww.com/epidem/pages/collectiondetails.aspx?TopicalCollectionId=4). The current manuscript treats this issue as if adjustment for multiple testing is always necessary and appropriate for both exploratory confirmatory analyses, and the language (e.g. “false positive results”) seems to indicate an underlying assumption that hypothesis testing is always being done (and the solution is to do less tests), which is not necessarily the case with much of cutting edge observational etiological epidemiologic research. The language should be adjusted to accommodate a more nuanced handling of these issues. Additionally, given its relevance and importance for the practice of science generally, the paper should probably discuss at least briefly how this debate regarding the use of p-values relates to the recommendations in the current paper.

Definition of exploratory analyses: do the authors include subgroup analyses of a main effect / evaluations of treatment effect heterogeneity across population subgroups as part of their definition? It seems these could be exploratory or confirmatory but that this is usually not specified. If considered exploratory, this should be stated explicitly, and when it is considered exploratory vs confirmatory, as it is a major subclass of exploratory analyses, and is especially relevant to health equity. I suspect
there may be multiple distinct classes of exploratory analyses that may require different methodological handling. This should be addressed explicitly in the paper – either that they should all be handled the same or some should be handled differently, which ones, and why.

The terms ill-suited, poorly-conceptualized, poorly-conducted, ad hoc, not rigorous, and similar are used frequently in referring to methodology that doesn’t handle exploratory analyses rigorously but what is meant by this is not well-defined as there are many ways in which a design or analysis can be poor, only some of which are discussed in this paper. It is also unclear if these terms refer to different weaknesses/problems or the same throughout. Throughout, there is a general message that exploratory analysis are not very rigorous and they should be made more rigorous but in precisely what respects and precisely what ways remains unclear. Recommend revising to more specific, precise, and with consistent terminology.

For each recommendation, I suggest adding more detail, being much more specific, and reviewing all the relevant/latest literature related to that topic. For example, I suggest adding more detail on how pre-specification is optimally done and how to ensure it is used and enforced. Simply pre-specifying something to yourself? Or registering a public protocol? If the latter, with what details in it? And who should compare the protocol to methods of the paper when the paper is submitted for publication?

As the paper highlights, lack of specification as confirmatory vs. exploratory is a major issue. I would say it is the main issue with exploratory analyses. Certainly, we can apply guidelines once research has been identified as exploratory, but what guidance can be provided on making sure exploratory research is consistently identified as exploratory? Consider discussing innovations in pre-registration—for example, that certain journals will deem a research question important and a study design adequate, so they publish the motivation and protocol for the study before it is conducted, and then guarantee they will publish the findings once they are available.

It is unclear if this paper is intended to be a commentary or a methodological guide. Much of the language errs on being a persuasive or opinion piece but I think it is meant to be a methods guide. If so, the language should be reined in to be a more balanced reporting of what is known, unknown, and established recommendations.

The paper is missing a review of existing literature that provides guidance on exploratory observational etiologic research. There may not be as much guidance as for trials but a simple google scholar search suggests there is relevant literature. At the very least, reporting guidelines (e.g. SHORT) for observational studies recommend declaring exploratory analyses as exploratory. There is also guidance on subgroup analyses / evaluations of treatment effect heterogeneity across subgroups that should be acknowledged if relevant. These areas of existing work and their gaps should be reviewed and discussed.

It is not explicitly said but it seems the authors are suggesting that exploratory analyses should have the same level of consideration for confounder control, functional forms, model specification, and assumptions as confirmatory analyses. Is that right? This should be clarified, and if so, I am not sure that I agree. Exploratory / preliminary studies are often done with less ability to control confounders and/or less rigorous data collection but serve to motivate the funding of larger studies that can do a better job. If I am interpreting the comment right, it suggests that studies should only be done if they can do the most excellent job possible given fairly unlimited resources, which is certainly not very reasonable and makes the perfect the enemy of the good. Suggest clarifying and justifying the stance here.

If the goal of this paper is to discuss optimal and rigorous statistical methods for handling exploratory analyses, a review/discussion of the latest advances in statistical methods for incorporating exploration and confirmation in a single study/analysis, e.g. sample splitting methods, seems essential.

Minor
Epi journal reports of associations - clarification: these numbers are the number of estimated measures of association presented as part of the primary analysis – is that right? Suggest making the language more precise to be clear.

It seems a further recommendation for reporting should be first clearly interpreting the results as exploratory, before then setting a clear future research agenda.

Do you have suggestions for ways for journals to operationalize crediting methodological rigor rather than the number or statistical significance of the results reported?

The section titled "Exploratory analyses require directions for the reader“ does not actually seem to indicate what specific pointers or directions should be given to readers and when.

“Rapid implementation of exploratory findings into policy can have unwarranted consequences.” Citation or support needed for this.

“the expected number of false positives (i.e., type I error rate) is likely inflated when statistical tests are not specified prior to data analysis or when the choice for a particular test depends on patterns in the data” – say why. Because more tests are likely to be done? Because the tests that are done won’t be adjusted for multiple testing?

“consensus on how to prevent false positive findings in exploratory settings has not been established” – needs citations

"combining another set of covariates in a model“ – unclear what is meant by this. Adding more covariates to an existing model? Relevance unclear - in what context would one do this?

Throughout, the language is a bit messy and wordy. It could use some copyediting.

In the conclusion I was expecting an answer to: When should exploratory results ever be applied in practice?

Additional Questions:
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Reviewer: 2

Recommendation:

Comments:
Thank you for letting me review this paper focused on exploratory analyses in etiological studies. The text is clearly written and provides a nice point of view on these analyses. The manuscript includes three separate (and almost independent) parts. First, the authors report a methodological research in the first issue of 2021 of several journals. They included studies assessing an etiologic research question and assessed the number of main, additional and sensitivity analyses. Second, they debate on the risks of these analyses (i.e. too rapid implementation) and on the rigor behind these analyses. Finally, they issue advices on how to conduct/report analyses.
Regarding the first part (i.e., the methodological research on the quantity of exploratory research in etiological research which is mainly presented in appendices)

1) please be consistent in the terms use and replace additional by exploratory
2) please precisely define the inclusion/exclusion criteria for studies (here it is said that they excluded studies that did not address an etiological question such as...). For example, are cross sectional mainly descriptive studies (e.g., description of cancer in the US) considered potentially etiological?
3) the authors refer in the main manuscript and in the appendices to a continuum of scrutiny. But in the end, it is unclear how to classify analyses between targeted and ad hoc (except for the extreme categories). For example, I am not sure how to interpret findings that are supported by the right hypothesis but tested with inappropriate methodology. That's why, I am not sure that the top part (nature of the analysis) and bottom part (methodological rigor) of Figure 1 should be presented on the same axis. Rather, I am wondering if they should not be presented as the x and y- axis of a plane.

Regarding the second part of the manuscript (i.e. debate on the risks of exploratory analyses). I am wondering if exploration in etiological research is at such high risk. The authors use as example the COVID-19 pandemic. But, in my opinion, this was more a problem for comparative effectiveness research. I would like more examples and references regarding the use of inappropriate results from etiological research in practice.

Regarding the final part (i.e., good practices). I think that problematic exploratory analyses are those that were not planned (even loosely planned). And the main risk is in the reporting, such as reporting them as specified analyses (or simply failing to report them as ad hoc analyses).

PS: It seems that figure 2 is missing
Finally, this is minor but I personally dislike the title. Indeed, the paper does not actually help in distinguishing pernicious ad hoc analyses but rather presents a very nice reflection on these analyses.

Additional Questions:
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Please enter your name: Viet Thi Tran

Job Title: Associate professor of Epidemiology

Institution: Université de Paris

Reimbursement for attending a symposium?: No
The authors raise important questions about the validity of results from exploratory studies, risks posed by their impact on clinical practice and the extra research costs of required confirmatory studies. They acknowledge the value of exploratory studies but note that there is little guidance on how exploratory research should be conducted and reported. It would be impossible to create universally-applicable detailed guidance because of how findings relate to specific research questions, but the authors have done well in providing some general recommendations which are presented in a table.

To provide evidence for their speculations, the authors analysed recent papers from four major American epidemiological journals. For each paper, they provided a summary of findings, including the type of finding according to their categorisation, the number of such results, the availability of a protocol and whether adjustment for multiple comparisons was done. However, I did not find these summaries particularly informative or persuasive – in particular, the number of results is not useful as an indicator of quality. Some results were for numerous subgroups by demographics or geographical areas or types of exposure, which do need caution in interpretation and selection for publication.
Some results were for different models, which could be interpreted as sensitivity analyses. Some results were for different durations or doses of exposure and could serve the principle of 'biological gradient', so providing more confidence in the plausibility of findings. Greater clarity relating to such issues would be helpful for readers.

Personally, I think that Hill’s principals of causality [PMC1898525] are fundamental to a discussion of this type and should be a core source of guidance for etiologic studies, so I am surprised that this source of good practice guidance is not even mentioned in the manuscript.

I was also quite disappointed not to find any recommendations for (or even discussion of) exploratory studies using machine learning techniques. As a novel approach, this has become more and more popular both among researchers and fund holders, sometimes one suspects with little attention to the potential pitfalls. A clinical pathway for such findings is substituted by an algorithm, which could be clearly described in a protocol. The results, however, may also be subject to residual confounding or be specific to a selected population. This is a very current, methodologically important issue and the manuscript would benefit from at least some coverage of the approach.

Additional Questions:
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