Dear Dr. Weill,

Thank you for sending us your paper. We sent it for external peer review and discussed it at our manuscript committee meeting. We are interested in proceeding with it, provided you are willing and able to revise your paper as explained below in the report from the manuscript meeting.

Please remember that the author list and order were finalised upon initial submission, and reviewers and editors judged the paper in light of this information, particularly regarding any competing interests. If authors are later added to a paper this process is subverted. In that case, we reserve the right to rescind any previous decision or return the paper to the review process. Please also remember that we reserve the right to require formation of an authorship group when there are a large number of authors.

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Dr Elizabeth Loder

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**Report from The BMJ’s manuscript committee meeting**

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

Present: Helen Macdonald (chair); Tim Cole (statistician); Joe Ross; Elizabeth Loder; Tim Feeney; Tiago Villanueva; Wim Weber; John Fletcher

Decision: Request revisions before final decision

* We thought this analysis was well done and the research question is of interest, with clinical implications. Since cyproterone is not available in the US, could you say more about where these findings could have clinical impact? It looks like this risk is already mentioned in the product label. Do you think your findings should lead to withdrawal of the product from markets where it remains available? We do note that there is updated safety information from EMA, which you might want to mention. https://www.ema.europa.eu/en/news/meeting-highlights-pharmacovigilance-risk-assessment-committee-prac-10-13-february-2020

* We think the abstract should provide a definition of what is high-dose cyproterone, as many women are on the low-dose cyproterone pill, which is not included in the definition of high dose, but may feel alarmed.
* The Supplementary Tables of the high dose cyproterone products available in different European countries are very useful but they should probably be included in the paper (perhaps as standard tables) as they are immensely useful.

* Can you please provide more information about the accuracy and completeness of the SNDS database?

* Exclusion with a serious illness needs to be better described.

* Table 1 gives mortality as 0.0% in both cases and controls, and the event of interest as 0.1% in both. Yet they are p < 0.0001 different, so some more decimal places would be useful.

* We wonder whether the most relevant application of this is in the transgender group, which you've excluded. We strongly encourage you to reconsider this decision and include an analysis of these patients, since there is clearly policy and clinical relevance there. If you are not able to do that, please expand your discussion of cyproterone use in this patient group, and possible risks and policy implications of your findings.

* Can you say more about the threshold you use? We don't think you tested for an interaction analysis but it looks like the dosage where we see an increase is not until 12 grams, which is a substantial dose. There is a small population on that dose. We worry it is misleading to cut at 3 grams. Looks like no increased risk at 3-6 grams. 6-12 leaning that way but not significant. Can you clarify whether the cutoff of 3 is the natural split between OC use and other uses in which case in policy terms it wouldn’t matter?

* Our patient editor was pleased with the statement you include in the paper.

Please revise your paper to respond to all of the comments by the editors and reviewers. The reviewer reports are available at the end of this letter, below.

In your response please provide, point by point, your replies to the comments made by the reviewers and the editors, explaining how and where you have dealt with them in the paper.

Comments from Reviewers

Reviewer: 1
Comments:
In this paper Weill et al. evaluated the risk of meningioma associated with prolonged exposure to high doses of cyproterone acetate in two French cohorts.

The event of interest evaluated by authors was intracranial meningioma that have undergone surgery or radiotherapy.

In this study authors demonstrates a strong, dose-dependent association between long-term exposure to CA and the risk of meningioma requiring invasive treatment.

As authors stated, a causal relationship between prolonged exposure to cyproterone acetate at high doses is highly likely given the presence of progesterone receptors in both normal arachnoid tissue and in meningiomas, as has been demonstrated for decades.

Such causal relationship is very strongly reinforced here by:
1) the strength of the association demonstrated
2) the clear dose-effect relationship,
3) the reduction of the risk of meningioma after discontinuation of cyproterone acetate treatment.
4) the specificity of certain tumour locations, especially the anterior skull base.

Major comments

1) The strength of the data provided here constitutes a major breakthrough in the field and raises an essential public health issue in countries where this drug is widely used: particularly in France (country where the prescription is wider and where the highest doses are prescribed) but also in European and south american countries. Authors should be thanked since the strength of their study will most likely lead to a change in clinical practice in these countries.

2) Main study cohort is well and clearly described but this is not the case for the complementary cohort. Authors must make an educational effort to explain clearly and carefully to the reader how these women were recruited and how they were followed. Similarly, Figure 1 is a bit confused regarding the origin and follow-up of this complementary cohort. It would have been clearer to make two independent panels each describing each specific cohort. In the same way the authors should explain much better in the introduction the rational of the use of the two cohorts.

3) Table 2 page 36: Incidence of meningioma according to exposure to cyproterone acetate: shows very impressive results. Authors should make an educational effort by making a figure clearly showing this incidence as a function of the cumulative dose. In this Table 2 the authors should clearly indicate on which cohort the exposed results are based (not clear).

4) Table 3: in a concern of pedagogy and medical importance the authors should make a figure showing the ages at which the diagnoses of meningioma were made (see also comment #5)

5) In page 24, lines 10-12 authors stated "........the majority of meningiomas occur after 10 to 30 years of exposure to CA." This sentence is of crucial clinical importance. It should be clearly be stated in the abstract.

6) Similarly authors should clearly indicate in the abstract that their study likely underestimates the overall incidence of intracranial meningiomas associated with cyproterone acetate as they clearly state on page 24, lines 47-56.

7) Table in supplemental material S9 is very important and would enhance the clarity of the study. It should be moved to the main Ms.

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Reviewer: 2
Comments:
Reviewer Comments: "Prolonged exposure to high doses of cyproterone acetate and the risk of meningioma in women: French cohort study on 253,777 exposed women."

1. This is a large observational cohort study which examines the risk of meningioma associated with exposure to high-dose cyproterone acetate (CA). The study is very well-presented, and the authors provide a compelling case for a causal relationship, including: the strength of association, the dose-effect relationship, biological plausibility and the reduction in risk after stopping CA. The authors also ruled out, to the best of their ability with the given data, the potential for indication bias, which is a major issue in pharmaco-epidemiology studies. The other major strength is the use of the large and representative cohort (and large numbers exposed), and use of time-varying drug
exposures in the analysis. The identification of the location of the meningiomas is another major strength.

2. The authors note in the introduction and discussion that a prior study noted an excess risk of meningioma in men using CA. The current study was restricted women. Given that CA is used in males, and men using CA would also likely be captured in the database, similar analyses in a male cohort would add to the generalizability and impact of this study.

3. The hazard ratios in Table 2 are adjusted for the use of estrogens. Please provide more details for how the use of estrogen was accounted for in the analyses (eg. binary variable, also time varying?, cumulative dose? etc). Estrogen use could also be summarized in Table 1.

4. Please provide details on other anti-androgen drugs (were these co-prescribed? is the effect specific to CA?).

5. While the use of one class of co-prescribed medications (i.e., estrogen use was accounted for in the analysis), the use of other concomitant medications is not provided (i.e., co-prescribed drugs for the same indications listed and co-prescribed drugs for other, even seemingly disparate indications). In Table 1, or as supplementary material, it would be helpful to provide a list of concomitant medications for each exposure group, for major classes of medications. If any major differences are noted, these could then be accounted for at the analytical stage.

6. A mediation analysis would be helpful to further disentangle the relationship between the drug indication, the drugs, and the outcome of interest. A causal diagram (eg. DAG) would also help in this regard. A causal diagram would also be useful to better understand the selected potential confounders and their hypothesized relationship with the exposure/outcome.

7. In the discussion, please provide background literature, if any, on adherence to CA medications, especially since this study used prescribing records to define the exposure.

8. Table 1 shows that the proportion of deaths in the “very slightly exposed” group was higher than in the exposed group. Although death was an exclusion factor for this study, it would be useful to complete a separate sensitivity analysis to examine time to death in the two exposure groups, as well as a comparison for cause of death in both groups.

9. In the methods, please provide further details for how the database used can be accessed (eg. procedure for data requests, if accessible to other countries, website to submit requests etc.).

10. The study does not include a comparison group with NO exposure to CA. Although this would require a modification to the study design given the cohort was defined by exposure to CA, it would be useful to see adjusted rates of meningioma in high exposed, slightly exposed, and no exposure at all, not to replace the current results, but to add to them.

11. In the methods, please provide more details of the women “excluded with a serious illness” (i.e., diagnostic codes).

12. It was stated that those undergoing male-to-female transitioning were excluded. Please provide rationale for this exclusion. The results would be more generalizable if it could also be shown that CA use is associated with meningioma in these individuals. Please also provide more details on how this exclusion criteria was defined.

13. Similarly, in the methods, the rationale is provided for excluding women with long-term disease (the authors state this is because CA may be used as a method of contraception).
14. There is a typo in Figure 1: "cohorte."

15. If these issues can be addressed, this work has important implications for patient safety.

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Institution: University of British Columbia
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A fee for speaking?: No
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Reviewer: 3
Comments: REVIEW BMJ-2020-054621 - Prolonged exposure to high doses of cyproterone acetate and risk of meningioma in women: French cohort study on 253,777 exposed women

Thank you for the opportunity to review BMJ 2020-054621. This is a highly interesting epidemiological study which is the first to provide highly powered data on an association between high-dose steroid therapy and treatment of meningiomas, with supportive data to suggest a particular effect in a subgroup of meningiomas. The findings are highly relevant, timely and fit with existing paradigms of biological causality and we believe the study has important contents, some of which would benefit from clarification or revision.

There are a number of issues that should be addressed in a revision.

1. It appears from the exclusion criteria (p 9, ln 17-29) that women with a meningioma diagnosis from 2006 until start of follow-up were excluded. It is necessary indeed to exclude patients with a known meningioma to avoid reverse causality bias (e.g. women with known meningioma in whom CA is indicated may be more likely to have the meningioma removed because of the presumed association, which led to the mentioned change in the labelling of CA, page 6 ln 45). Hence,
   1. Please comment on the risk of including patients already known with a meningioma and the subsequent risk of reverse causality bias.
   2. Is there any chance to retrieve meningioma diagnoses of the cohort members given before 2006?

2. What was the rationale to choose an exposure-threshold of 3 g CA (50 mg daily for min. six months)?

3. In the results section page 14, ln 38-42, it reads as if the age group 25-34 was used as a reference, and not the youngest age group with the presumed lowest risk (below 25 years of age). Please explain or justify – or is it a typing error?

4. Please analyse whether the association of anatomical location and cumulative CA exposure could reflect reverse causality; would a longer treatment time increase the likelihood that a treating physician would obtain brain imaging? Is it more likely that a meningioma adjacent to the optic apparatus gets detected early and provides a location-related bias? Is it more likely that a convexity meningioma gets operated due to a relatively accessible location? Please, discuss these possibilities.

5. Age- and gender specific incidence rates per 100,000 patient-years were published by Wiemels J et al., Journal of Neurooncology 2010, fig 1 (quoted in the article). Please compare the incidence rates in the present study to those found by Wiemels et al in the discussion.

6. From a scientific perspective, it is necessary to remain as objective as possible – especially in the age of “alternative facts”. The discussion in the second half of “Comparison – Risk and causality”, p 18 is more rhetorical than scientific and should be revised and partly deleted; the authors are recommended to “kill their darling”.

   The objective is to criticize a study by Cea-Soriano, but the arguments are not relevant:
   1. The following sentence is irrelevant: “the finding was highlighted in the conclusion of the abstract” Whether a finding was to be included in the abstract is a matter for the original authors and editors – it is irrelevant to discuss in this context.
   2. This section creates an argument based on “guilt by association”: “The study was sponsored by a drug company, the initial marketing authorization holder of CA in Europe. Furthermore, two of the four authors were salaried employees of this company and two
others received unrestricted grants from the company. Experience has shown that conflicts of interest with a drug company can influence the choice of methods, study populations and finally the results, particularly in a study of the relationships between hormones and severe adverse effects [27].

In a scientific publication the authors need to reverse the argumentation. First, they must demonstrate that the disagreement of studies actually reflected inferior choices of methods, study populations and results by Cea-Soriano. Second, they can offer an alleged conflict of interest as an explanation. It would make better scientific sense to conclude that the three studies are not comparable.

Cea-Sorianos findings may be valid for a population with low exposure to CA (especially the findings in males were important), while the three studies together may offer a coherent body of epidemiological evidence when the differences of populations and exposure are accounted for.

7. P. 18: “The three main identified risk factors”; Please revise and rephrase. Genetic factors (NF-2) and ionizing radiation are well established risk factors (although only accounting for 1-2 % of all meningiomas, while sex-hormone exposure is controversial, as disclosed in the following section of the discussion. Please add clarity to this section; actually your finding of a possible subgroup effect of sex-hormones and the lack of large-scale scale data on differential exposure to differently composed sex-steroids are the two main explanatory models for the conflicting findings of sex-hormone exposure and risk of meningioma.

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Please enter your name: Tiit Mathiesen

Job Title: Professor

Institution: University of Copenhagen / Rigshospitalet

Reimbursement for attending a symposium?: Yes

A fee for speaking?: Yes
Reviewer: 4
Comments:
This French cohort study followed women initiating treatment with cyproterone acetate (CA) from January 1st, 2007 until December 31st, 2014, and followed until end of 2015 for surgery or radiation therapy of meningioma. The exposed women were stratified into those receiving less than 3 g in total, and those having received 3 or more g. Exposure data was achieved from the French national health data system (SNDS) as were diagnoses of meningioma and surgical/radiologic treatment of meningioma. SNDS is an insurance database. Women with chronic diseases at study start or after study start before first prescription of CA were excluded.

Among all exposed, 89 developed a meningioma. The study demonstrated a strong correlation between the total dose of CA received and the risk of meningioma; <3g ~ 4.5/100,000 women-years and ≥3 g ~ 23.8/100,000 women-years. The corresponding HR with <3g as reference was for 36-60g 11.3 (5.8-22.2) and for doses >60g a HR of 21.7 (10.8-43.5). Among those having received >3g, the HR one year after discontinuing use of CA was 1.8 (1.0-3.2).

General comments
This study is the most comprehensive study made so far to evaluate the risk of meningioma in women exposed for different total doses of CA. The issue is important because CA is used off-label especially in France, and meningioma despite a benign tumor may have devastating consequences for the patients. Another important aspect is that discontinuation of CA use has a high chance of ceasing the tumor growth in women already having developed a meningioma.

Both exposure information and end point definition ensure a high validity for real exposure and real events. The study is complicated, as to different cohorts are followed; those beginning their user after 2006 and those already in treatment in 2006, with main emphasis on the former, which is a correct choice despite much more end points in the latter. Another complication is that only re-imbursed patients are included in SNDS. I think the first section on page 8 (Data source), should give a little more information about the limitations of the database e.g. that users of hormonal contraception with CA are not included, because it is not reimbursed. Thereby several points become more logic and understandable. E.g. why this study could not compare the risk in users of CA with the risk in non-users instead of users of low total dose CA.

Nevertheless, the study is well described. The introduction appropriate in length, method section is long, but necessarily so, to understand the design and methods. Result section
also long despite large tables, but again logically set up and referred. The long section of anatomical localization of the meningioma is interesting but could perhaps be shortened with reference to Table 3. This is not a trivial finding, because skull.base tumors are much more difficult to treat than tumors located in the outer part of skull.

The reference group of women having used less than 3g CA in total had a follow-up period of 3.8 years as compared to 2.1 years for the exposed group. Thereby the reference group had 81% more follow-up time to develop a meningioma than had the “exposed” group. That circumstance is expected to underestimate the impact of CA for meningioma development in the “exposed” group. Please comment on that circumstance. Normally follow-up indicates the length of time after exposure start until end of study period. Here follow-up means length of use plus one year for the exposed group and another thing for the “very slightly exposed group”.

Discussion is appropriate, including going through previous studies on the matter. Reference list seems updated and appropriate in size.

Specific minor points
Page 14 line 31-33: A mean duration of follow-up of 2.1 year is surprisingly short considering the study period to be eight years. That suggests the vast majority of users of CA began their use late in the study period. But according to Table 1, the use of CA was decreasing by time. Please explain.

Page 24, first line: 50 is 25-fold higher than 2. But 2 is not 25-fold lower than 50. Write instead that

Table 3: I suggest that all information after “anatomical location of meningioma” in 6 groups are being left out, as the text is sufficiently clear to describe the other points.

Supplementary material S3: The headline indicates “List of ATC classes of oestrogens”. What the table shows is different types of progestogens combined with unspecified types of oestrogen. Please make consistency between headline and table content or drop the table. This table should only show the types of estrogen prescribed together with CA, according to second bullet on page 11.

Supplementary Material S9: A “zero” is missing in the number of exposure years for the group of 60g or higher.

In conclusion this study brings convincing evidence of a causal and substantial influence of CA on the risk of developing meningioma in women of reproductive age. The message is important to get out as concerning many women take CA off-label.

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Use of hormone modulators have been on the rise since the introduction of the contraceptive pill. There is ongoing research on the long-term effects of this treatments which more often are mainly used by females. Meningiomas are known to have a higher prevalence in females. This study answers a very useful question on the long-term effects of cyproterone and meningiomas in the female population. It is well structured with a clear description of the study methodology. The use of the SNDS offered a very unique opportunity to achieve a good sample size in both arms and reduce sampling errors by using a large national database. The SNDS also is unique in enabling the investigators to study the prescribing patterns for Cyproterone in the French population.

It is interesting that the studied population (France) not only had a high incidence of off-label prescribing but also had higher dose prescriptions compared to the rest of Europe. The association of operated meningiomas and higher doses of Cyproterone may be because Cyproterone promotes meningioma development. An alternative explanation may be that the patients underlying condition may be linked to the incidence/growth of meningiomas. Most of the prescribing in this group were by gynaecologists. It may be that the hormonal changes in the presenting primary conditions (which in themselves may have needed higher CA doses for treatment) are the reason for the meningiomas and as such the Cyproterone may be an association rather than a cause.

Overall, it is a well-designed and written study which contributes significantly to the ongoing debate of the relationship between CA and meningiomas. The authors have been
balanced in their conclusions having explained the limitations of the study model they have used. It is well referenced to the current literature. I recommend the paper for publications with no reservations.

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