Author's response to reviews

Title: Influence of family size and birth order on risk of cancer: a population-based study

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Author's response to reviews: see over
Dear Editor,

With this letter we submit the revised manuscript “Influence of family size and birth order on risk of cancer: a population-based study” for publication in BMC Cancer.

Please find below the point-by-point response to the reviewer's comments:

Reviewer 2

Minor Essential Revisions

1. Page 1. In the abstract section, the Results and the Conclusion parts are not consistent. The authors concluded that their findings suggest that the effect of birth order decreases from early to late adulthood for lung and endometrial cancer. However, none of these results were presented before. The authors may need to revise these parts to make the presentation of the abstract more rigorous and precise.

   - I included the results in the Results part.

2. Page 5. In the end of the first paragraph, the author described “To analyze these effects from childhood to adulthood the analysis was stratified for age at diagnosis less and at least 20 years”. Because childhood cancer and adulthood cancer are normally different types of cancers, thus, this kind of analysis does not truly answer the proposed question. I would suggest the authors reconsider if they need to present the analysis and the results (although not shown) in this manuscript.

   - I deleted the part of the stratified analysis by age 20 as it was not necessary to present this results.

3. Page 5. Second paragraph about the codes for cancer sites. I couldn’t find a clue why the authors only presented the codes for several types of cancer but not for others. If the authors can give a complete list of all cancer types studied in this paper that will help the readers to understand the whole picture.

   - I included a column in the tables where all the ICD-7 codes are listed. The grouped codes I presented separately in the methods part.

4. Page 7. Paragraph 2, the authors listed the relative risk of thyroid cancer for different birth order. Since the data was not shown, the P for trend may help the readers to further understand the results.

   - I calculated the P for trend using a Jonckheere-Terpstra test which is a nonparametric test for ordered differences among classes.
5. Page 7. Paragraph 4, “Smaller family size was negatively associated with stomach cancer…….”. This sentence is confusing regarding bigger family size increase or decrease the risk of stomach cancer. Suggest the author use “Family size was positively associated with stomach cancer……”.

- I changed this sentence to "Family size was positively associated with stomach cancer...".

6. Page 8. The results for Table 5 were presented after the results for the figures, which is easy to make the readers confused after reading the results for the figures. The results for Table 5 should be presented after the results for Table 4 and before Figure 1.

- I changed the order of the results part.

7. Page 8. Again, I would suggest that the authors delete the stratification analysis by age 20. It is not informative in this context.

- I deleted the part about the stratified analysis by age 20.

8. Table 3 and Table 4. For “Squamous cell”, the authors may want to make it clear as “Squamous cell skin cancer”.

- I changed it to "Squamous cell skin cancer" in Table 3 and Table 4.

9. Figure 1. For all the cancer sites in the figures, the authors used “1” as the reference group except for the stomach cancer. I would suggest presenting the figures consistently and changing the reference group for stomach cancer to be “1” for both birth order and family size.

- As I wanted to present results about the effect of family size stratified for birth order, it was necessary to set the largest family size group as a reference (to make it possible to compare first born, with second-born, third-or fourth-born to at least fifth-born children - this was not possible using one-child families as a reference).

**Reviewer 3**

The paper is not improved enough. Some of my previous comments should still be accounted for.

2.b: Do you mean that all the positive results were similar when the cases with affected parents were included? If so, this is an interesting result and it should be added at the end of the Results section. Even if it concerns a subset of results, it is still noteworthy.

- The aim was to look at the effect of birth order and family size. To avoid any confounding effect by parental cancer cases we excluded the individuals having affected parents. As some positive results were similar but others differed, it is not possible to generalize the effects.
2.c: I still think that using 1% confidence intervals is not sufficient to account for multiple testing. Even if you keep it, you have to discuss further the issue of multiple testing in the Discussion section.

- I deleted the information on 1% confidence intervals as the information on 5% confidence intervals is enough.

2.d: I am convinced that overall the power is very good, but for some cancer sites such as stomach cancer (see 3.c below) the numbers may be small when stratifying before/after 50 years of age. For these sites, information on power may still be useful.

- Even if I look at the power for cancer sites with small numbers in the stratified analysis, I get power of at least 0.9.

4.a: The association with CLL should be given in the text.

- I included the results.

4.b: Please, help the reader to distinguish between birth order and family size, and explain how their relationship with SES changes with age in your data.

- We have more information on the SES of older people in our data. The information is more detailed but the overall distribution does not change over time.

4.d: I still think that figures and tables are redundant and that tables are far more useful. Having a consistent presentation from table to table is necessary, and the present inversion of columns and lines between tables is misleading.

- The graphs show the effect changing from early to late adulthood. This can be seen more clearly in a graph than in tables alone.

5.a: The discussion on endometrial cancer is confused and misleading (second paragraph page 9): the 2 first sentences of the paragraph contradict each other, and there is no actual difference in the relationships before and after 50 years old. The explanation on SES is not clear either (specify “obesity is associated with lower socioeconomic status”), and the last sentence of the paragraph should be dropped or clarified.

- I dropped the last sentence of the paragraph and corrected the second sentence that it does not contradict the first one.

Sincerely yours,

Melanie Bevier (on behalf of the co-authors)

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