Author's response to reviews

Title: Exposure to animals and risk of oligoarticular juvenile idiopathic arthritis: a multicenter case-control study

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Author's response to reviews: see over
Answer to the reviewers:

First of all we would like to thank the reviewers for their critical and helpful comments and suggestions.

Reviewer’s report:

It was a privilege to review this most interesting study. My comments below are mostly discretionary, but I hope they will be taken into consideration nonetheless.

Abstract; Instead of ‘Neither place of living (urban vs. rural area), living on a farm, nor regular farm animal (adjusted odds ratio 0.79; 95% confidence interval 0.42-1.47) or pet contact (0.79; 0.55-1.14) during infancy were related to case status.’ I would say (because the estimates are imprecise) “Neither place of living (urban vs. rural area), living on a farm, nor regular farm animal (adjusted odds ratio 0.79; 95% confidence interval 0.42-1.47) or pet contact (0.79; 0.55-1.14) during infancy were clearly related to case status.”

Answer to the reviewer: We have changed the sentence as proposed by the reviewer.

Introduction

I find the introduction too long; in the medical journals that I am familiar with the introduction is usually only a few paragraphs. What is currently in the introduction would be better placed, in my view, in the discussion.

Answer to the reviewer: We have shortened the introduction (page 3).

Methods:

1. “The following variables were included as potential confounders / predictors: age on January 1st 2006, gender (male/female), allergic rhinitis (yes/no), period of breast feeding (<6 months / >6 months), highest parental level of education (? vs. < 12 years of schooling), and maternal smoking during pregnancy (yes/no).”

I acknowledge that you should include whatever factors you think may be true confounders that is, related to both exposure and outcome. So I understand why you included sex, breastfeeding, education, and smoking, as theoretically these all might be related to likelihood of the family owning a dog. (Some of these might also be effect modifiers). And age should be controlled for since it might affect recall. However, I don’t think allergic rhinitis should be in the model, as I do not see how it could be a confounder. In fact, a confounder must not be an effect of the exposure, and there is in fact evidence that allergic rhinitis may be linked to the exposures under study. (To explain this another way, if you were going to study smoking and lung cancer, you wouldn’t control for heart disease.) So I would suggest the authors repeat the analyses and leave out allergic rhinitis.

Answer to the reviewer: We have included allergic rhinitis in the model as this is a relevant predictor for OA JIA which we intended to evaluate.
2. Regarding the use of ‘gender’, this term is sociological, don’t you think the term ‘sex’ (which is medical or physiologic) is more appropriate?

Answer to the reviewer: We have changed the term “gender” into “sex” as proposed by the reviewer.

Results

1. P. 7 In the bivariate analyses, only ever contact with dogs ....were weakly associated with case status.” Better to clarify as ‘were weakly inversely associated“ or say there was a trend for less contact in the JIA patients.

Answer to the reviewer: We have added “inversely” to the sentence “For allergic diseases, the “hygiene hypothesis” has been well established.” I think this is controversial. It might be better to say something like “For allergic diseases, some have suggested that the prevalence of allergic disorders may be attributable to a reduced exposure to microbial agents (the ‘hygiene hypothesis’).” Or something like that.

Answer to the reviewer: We have reworded the sentence in the revised version on p. 3: “For allergic diseases, some have suggested that the development of atopic diseases is facilitated by a decreasing level of microbial exposure in early life (“hygiene hypothesis) [15,16].”

Discussion:

1. “Due to a relative low number of children newly diagnosed with OA JIA, we could not restrict our study to incident cases …In result, recall bias might have taken place. Due to a relative low number of children newly diagnosed with OA JIA, we could not restrict our study to incident cases [35]. Likewise, children mostly undergo strabismus surgery at around age 6 years. In result, recall bias might have taken place. As the parents of cases and controls were most likely not aware of a potential association under study no major bias is anticipated to result from this selection of patients.”

a. As I am sure the authors are aware, the study of prevalent cases can introduce another kind of bias, which may or may not be important, but could be mentioned. That is, if the exposure of interest IS in fact related to the disease under study, and in fact causes VERY SEVERE disease of poor prognosis (e.g. leading to early demise), then in fact you may see NO association, or even an inverse association. Some forms of JIA can be life-threatening, but not usually, I think, OA JIA. Thus I doubt this possibility caused an important bias. However, I think it might be worth mentioning this possibility.

b. Also regarding recall bias, this can sometimes cause a bias if it is differential (that is, different for cases or controls) but often it can just be incorrect recall due to the passage of time, which I think would likely be non-differential among cases and controls. That would lead to a bias towards the null, would it not? (On the other hand, since your controls were older, more time would have passed since infancy, so maybe the recollections of past exposures would be less reliable in the controls vs. the cases….but I am not sure what effect that might have.)
Answer to the reviewer: We have added the aspect to the discussion on p.9, 3rd paragraph.

2. “The fact that previous studies have indicated a similar association gives further evidence for an inverse association between allergic rhinitis and JIA [11-13].” Here, I think you can re-write this to indicate that the inverse association is already well-established, and appears to relate to underlying differences in genetic make-up.

Answer to the reviewer: We have rewritten this aspect in the revised version on page 8.

3. I think you would do well to try to focus the discussion more on the results and their implications. As it is, I think the discussion is too long. What would be better, in my opinion, is if you merge some of what you include in the introduction, with the discussion, and try to streamline it.

Answer to the reviewer. We have revised the discussion.

Reviewer's report:
The question posed by the authors is well defined: this article reports a case-control study investigating the role of early exposure to animal in the onset of oligoarticular juvenile idiopathic arthritis (OJIA).

The method is appropriate and well described: although I am not a methodologist, case-control study is a suitable way to evaluate the role of a single outcome measure: here early exposure to animal in a rare disease such as OJIA. The methods are well described.

Data: The data are also well reported. I did not identify any differential measurement bias nor sampling bias. The cases and the controls have not been obtained from the same hospital but cases and controls come from the same area and therefore are expected to have a similar exposure. However, a control group from the same hospital would have been methodologically better but apparently not feasible.

Limitation at children greater than 6 years of age makes the case group less representative of the disease as patients with OJIA are expected to be very young as you can see in table 1 (age at diagnosis). However, I don't think that this makes the sample of cases unrepresentative with respect to the risk factor being studied. Similarly, I would have chosen patients caucasian (instead of born in Germany + ethnicity is not detailed) as genetic background thus response to infection/exposure might be different. Similarly, I would have chosen ANA (antinuclear antibody) positive JIA a supposedly even more genetically homogenous group of OJIA to be able to catch the role of exposure.

In the statistical analysis (again I am not a methodologist), the authors should explain/justify why they chose age, gender, allergic rhinitis, period of breastfeeding, highest parental level of education and maternal smoking as potential confounders/predictors.

Answer to the reviewer: We have added some sentences into the revised version on page 6:
“Level of education, breastfeeding and smoking were included as they are relevant factors regarding socioeconomic status and therefore give information about different lifestyles (e.g. likelihood of living on a farm). Allergic rhinitis was included as it is a known predictor in case of JIA.”

The authors should explain why they did not match cases and controls for age and gender. The difference in gender and age between the two populations has been taken into account with adjustment in the multivariate analysis.

**Answer to the reviewer:** We already discussed this aspect in the manuscript on p. 9: We did not match cases and controls because matching results in a loss of potential study subjects and thus reduces the efficiency of a study. Furthermore, matching may even result in greater difficulty in controlling for additional confounders [36].

In the results, the authors should clarify why they perform a bivariate analysis. Reporting and data deposition is performed under the relevant standards.

**Answer to the reviewer:** We did bivariate analysis to investigate first associations between the exposure variables and the outcome variables.

The discussion details adequately the potential bias and the justification not to perform matching between cases and controls. It also discusses in the light of other publications the role of allergic rhinitis and the predictors not replicated in this study. All is well supported by the data. The limitation of the work is clearly stated. Authors clearly acknowledge related works.