Author's response to reviews

Title: Allergic conditions and risk of hematological malignancies in adults: a cohort study

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Author's response to reviews: see over
Dear Editors:

We thank you for giving us the opportunity to revise our manuscript entitled Allergic conditions and risk of hematological malignancies in adults: a cohort study. We think that our responses to the reviewers’ comments have improved the manuscript.

Sincerely,

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Lin Fritschi
The percentage of people reporting allergic conditions has been added in Table 1.

1. The various hematological malignancies are different diseases with different etiologies and the same exposure can increase the risk of developing one disorder but decrease the risk of developing another. Therefore it is not meaningful to analyze all hematological diseases combined. E g, for leukemia, we found an elevated risk associated with hives whereas no such increase was observed for myeloma or NHL.

2. CLL is the most common type of leukemia and in our material the number of cases was big enough to offer the chance of separate analysis, as CLL constitutes half of the leukemia cases. CLL is generally regarded as separate from the other leukemias; the WHO classification from 2001 considers it more closely related to small cell lymphocytic lymphoma than to the other leukemias. Furthermore, previous studies indicate that environmental exposure is of less importance for CLL than for the other leukemias.

3. We use the twin cohort as an ordinary cohort without consideration of twin status. There is no reason that we can see that the results from the twin cohort would not be generalizable to the general population, especially since all comparisons are made within the cohort. There are several other studies based on the Swedish Twin Registry analysed with a cohort study design and published in well renowned international journals (see for example: Terry et al. Fatty fish consumption and risk of prostate cancer, Lancet. 2001 Jun 2;357(9270):1764-6. Moradi T et al. Physical activity and risk for breast cancer a prospective cohort study among Swedish twins, Int J Cancer. 2002 Jul 1;100(1):76-81. Jonsson F et al. Obesity and
hormone-dependent tumors: cohort and co-twin control studies based on the Swedish Twin Registry, Int J Cancer. 2003 Sep 10;106(4):594-9). We don’t have any information about the prevalence of allergic conditions in twins compared to non-twins. To be able to compare the prevalence in our study to that in the general population we would have needed to ask the same questions to a sample of the general population back in 1967, which wasn’t done. However, all associations reported in our study are based on comparisons within the twin cohort; no comparisons are made to the general population.

4. The text has been revised according to reviewer’s comments (page 12).

Brigitte Schlehofer
Method section: The text has been revised according to reviewer’s comments (pages 4-6). We have clarified the description of the cohort as pairs and individuals, respectively, and response rates. We have also clarified that the twin cohort was used as a population-based cohort without considering twin status.

There was no concordance within the groups of leukemia, NHL or myeloma, but two concordant pairs for hematological malignancies. For allergic conditions, 496 pairs were concordant.

More precise information about exposure assessment has been added in the manuscript on page 6, addressing all of the reviewer’s queries. Information about missing values on the questions about allergic conditions is available in Table 1.

Table 2 and Table 3 have been revised according to reviewer’s comments (pages 16-17).

Jacqueline Clavel
In our first version of this manuscript it might not have been fully clear that the twin cohort was used as a population-based cohort without considering twin status, and that the purpose was not to investigate the genetic influence on the risk for hematological malignancies, allergic conditions, or observed associations. This has now been clarified on page 5. Many of this reviewer’s comments are related to twin status or specific twin analyses aiming at elucidating the genetic influences, which is probably a result of a misunderstanding of how the cohort has been used, and the purpose of the study.

1a. The concordance between twins is not relevant for the purpose of this paper as it relates to the heritability. The statistical methods chosen for our study adjust for dependencies within pairs. There was no concordance within the groups of leukemia, NHL or myeloma, but two concordant pairs for hematological malignancies. For allergic conditions, 496 pairs were concordant.

1b. The text has been revised according to the reviewer’s comments (page 7).

1c. The statistical method we have used was chosen exactly for the purpose to take the relationships within twin pairs into account, to ensure that confidence intervals were not erroneously narrowed due to dependencies within twin pairs. The shared frailty model suggested by the reviewer would have been appropriate if the purpose of the study was to estimate the heritability, but this was not our aim. The cohort was used as a sample of the general population disregarding the twin property, but with adjustments for dependencies within pairs. We chose the Cox model because it is an established method used for analyses of cohort studies.

2a. The query is ambiguously formulated. It is not obvious whether the referee is interested in the shift over calendar years in incidence in allergy and hematological malignancies in a) the
study base of twins, or b) in the general Swedish population. The option a) is rather pointless as the study design uses the cumulative incidence of allergy at start of observation period, and give no information about incidence. Moreover, the shift in tumor incidence over the calendar-years in the study base can only give meaningful information if comparisons are made with the general population. Considering option b) there are no data available that can give allergy incidence data over different calendar-years for the Swedish population. The change in incidence in hematological malignancies over the calendar years for the general Swedish population can easily be provided, but the relevance of such data in the present manuscript is not obvious.

2b. We suppose that you can introduce a dichotomized variable for calendar year period in the Cox model, but we doubt that it is a very good idea. First, calendar year period must primarily be regarded as a potential effect modifier and not as a confounder, and therefore a stratified analysis is more reasonable than inclusion of a new covariate in the regression model. Second, considering the low numbers involved, we doubt that the statistical power will allow stratified analyses.

3a. The referee might have missed the point that we are not using incidence rate but cumulative incidence data on allergy. Thus, it is clearly stated how many subjects at start of observation period had or had not a history of allergy. The requested person-years can of course be calculated, but it is doubtful whether it will enhance the readers understanding. The total number of subjects has been added to Table 1, which makes it possible to calculate missing values for the separate allergic conditions. We could of course also add an extra column to the table with the number of missing values, but we felt that this would make the Table very busy.

3b. This is already given in the Methods section.

3c. It seems that the referee suspects that the study base may not be representative for the general population, and therefore wants information on major causes of death. It is an easy task to list major causes of death, but if this information should be meaningful for the reader, it has to be compared with similar figures for the general population, taking into account, gender, age-distribution and calendar-years of follow up. Thus, a traditional cohort analysis, with SMR values is needed. However, this is quite a task and it seems hard to advocate why to put so much emphasis (including complementary text and tables) on this in the revised manuscript.

4. Smoking has been suggested to increase the risk of leukemia, particularly for AML. Alcohol consumption has not generally been linked to an increased risk of leukemia, but there are a few studies where an increased risk for a hematological malignancy has been seen (Schottenfeld D, Fraumeni JF (eds.): Cancer Epidemiology and Prevention, 2nd edn. New York, Oxford: Oxford University Press; 1996). Since information about alcohol and smoking was available in our material, we used the opportunity to control for them.

5a. The sentence about the antigenic stimulation hypothesis has been clarified (page 3). Considering that allergic reactions are mediated primarily via lymphocytes, an elevated risk could have been expected to be most pronounced for lymphatic leukemia. However, the immune system is complex. Activation of lymphocytes leads to increased production of interleukins, e.g. IL-1, IL-3 and IL-6, which are involved in inducing proliferation of multipotent stem cells in the bone marrow, as well as in stimulating proliferation of granulocytes. Hence, excessive lymphocyte activation also affects the myelopoietic system.

5b. The question is now cited in the manuscript (page 6).
5c. We have not analysed whether allergy is related to other causes of death in the cohort for several reasons. First, this was not the purpose of the study and therefore we did not obtain information about mortality. Second, including such information would increase the size of the paper considerably. We doubt that such information would change the conclusions in our paper.

6. Text has been revised according to reviewer’s comments (pages 3-4).