Reviewer's report

Title: Validity of information on atopic disease and other illness in young children reported by parents in a prospective birth cohort study

Version: 1 Date: 15 May 2012

Reviewer: Carel Thijs

Reviewer's report:

General remarks

This article demonstrates the sensitivity (completeness, underreporting) of atopic and other diagnoses until age three years in the COPSAC birth cohort study, a well known Danish cohort study with its own niche and strength among the many birth cohort studies on allergy and asthma. The results are valuable for other cohorts on the the topics, for the interpretation of the results of the COPSAC study and similar cohort studies, and for the design of new cohort studies.

The article however does not present result on specificity (overreporting, misdiagnosing). The authors admit this in the Discussion, nevertheless it is not quite satisfactory since specificity is indeed an issue in epidemiological studies. The authors seem to assume that GP's diagnoses are suitable as a gold standard to determine sensitivity of COPSAC diagnoses, but not suitable to determine specificity. No clear arguments are given for this assumption (see also my comment on sensitivity and specificity of GP's diagnoses in the Discussion section, below; this is especially important for the diagnosis of asthma, as argued below).

The order of the sections (Methods section placed at the end of the article) has some disadvantages: in the Results and in the Discussion it is not always clear how events and atopic diagnoses were defined, because the necessary information about the design and execution of the COPSAC study is only given later in the Methods section. Therefore, please consider a conventional order (Methods before Results) if possible, otherwise give some more essential details in the Introduction or Results. See my comments on unclarities below.

Discretionary and Minor Essential Revisions

1. Introduction

line 65: the next sentence is not clear to me, please reformulate: "Children that are diagnosed and treated by other physicians without our knowledge would potentially compromise the quality of our data." This sentence can easily be misunderstood when the reader does not know that children were seen by study doctors (this is only mentionned later in the Methods); e.g. where the COPSAC doctors also the treating physicians and the ones who informed the GP about the asthma diagnosis and treatment; or were other physicians (GPs or
paediatricians?) the treating doctors and did the parents report on those doctor's diagnosis and treatment?

2. Results, line 82

How are "medical events" defined? Please clarify if a repeated report of the one and the same continuing disease episode at two visits counted as one or two events? And the other way around, are repeated episodes during one period between interviews counted as separate events?

3.

Point 2 is especially important for wheeze and asthma. Was asthma considered a life-time diagnosis (in other words is the no. of asthma events (48 in Table 1) reflecting the total number of children in the cohort with asthma ever), or is it reflecting distinct episodes of asthmatic symptoms (so that one child could contribute more than one asthma event)? Since no asthma diagnoses were missed by COPSAC this implies that repeated visits at the GPs (for instance for asthma medication follow-ups) were not counted as multiple events. This adds to the confusion and therefore I would suggest to explain clearly what is meant by asthma events and a diagnosis of asthma.

4.

For asthma there is another point: it is questionnable whether a diagnosis of asthma can reliably be made before the age of about 6 years. My own experience is that this is even known by parents, since sometimes in our studies we encountered that parents reported in the margin of the ISAAC asthma core questions that "my doctor does not diagnose asthma before the age of 6". If this was common medical practice in Denmark too, the fact that no asthma diagnosis were missed by COPSAC may simply be due to the GPs not using this diagnostic label under age 3 at all. For that reason alone it would be informative if wheeze was added as a diagnostic category in the table. It is puzzling that wheeze (other than the repeated and persistent wheeze that was required for a diagnosis of asthma) is absent from the table; one would expect that many children would have been seen by the GP with wheeze episodes that do not comply with the stringent criteria of asthma as defined by COPSAC.

5.

For asthma it would be also be informative to know the range of severity (in the Methods criteria for a study diagnosis of asthma are given, but this seems to be a broad range).

6.

The table gives the no. of events regardless how they are distributed over children; it would also be informative to have an analysis at the child level, at least for the atopic diseases: how many children had a diagnosis of atopic dermatitis or rhinitis ever in the first three years (this can easily be added to the table without much expanding it).
7. Methods line 231:
"The symptom character was judged by the doctor to be typical of asthma ..": it is not clear to me whether this was a requirement for the COPSAC diagnosis of asthma, or whether persistent wheeze was sufficient for the COPSAC diagnosis of asthma.

8. Methods line 242:
"Allergic rhinitis was diagnosed in children with sensitization to inhaled allergens clearly related to the symptomatic periods.": This sentence is unclear to me: the word sensitization suggests that this was tested by skin prick or specific IgE tests against aeroallergens, the word "inhaled allergens" suggests a challenge test by allergen inhalation, and "symptomatic periods" seems to refer to seasonal symptoms but does not describe the symptoms themselves (rhinitis without fever? rhinoconjunctivitis?); or does it just mean that allergic rhinitis was diagnosed if there was a history of seasonal rhinoconjunctivitis or rhinoconjunctivitis associated with alleged indoor allergen exposure? Please clarify.

9. Methods
What measures were taken to ensure that the coding of GPs data was done independently from the COPSAC diagnosis? Who did the coding of GP data, was it done by one observer or two (and if so, independently, and was agreement checked?), were they blinded for the COPSAC data? Since for some atopic diseases the classification is difficult and arbitrary such independence is important for the credibility of the results, especially for the finding that atopic disease where 100% complete. For instance, where the 13 cases of "dermatitis" reported by GPs and missed by COPSAC really different from "atopic dermatitis"?

10. I miss information on the compliance with study visits. This would be valuable information, since the chance of missing a diagnosis is probably bigger when one or more visits were missed; given that no diagnoses were missed it is important for future investigators to know this to be able to replicate this high sensitivity.

11. Discussion line 120:
"Inter-observer differences have revealed satisfactory agreements between GPs around 80%[10, 11] and GP records therefore seems like a very sensitive, but probably not very specific source of health information." This sentence seems to justify why the authors only looked to sensitivity of COPSAC diagnoses and not specificity (false positive diagnoses cannot be identified by GP’s diagnoses if GP’s diagnoses are not specific).
But since the cited studies [10 and 11] only report interobserver differences no straightforward conclusion can be drawn on sensitivity and specificity of GP’s diagnoses. Please nuance this. I can accept that over-reporting of symptoms was
not addressed (as admitted in line 164) but over-reporting of doctor's diagnosis (specificity) seems quite possible and it would be worthwhile to have this reported too.

12.
Table 1: a confidence interval for the completeness of Atopic Diseases would be informative (given that the completeness is 100%, it should be an exact one-sided lower confidence limit, e.g. a 95% or 97.5% limit).

13.
Abstract: the year(s) of birth of the children would be informative.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests'