Reviewer's report

Title: Temporal changes in the prevalence of childhood asthma and allergies in urban and rural areas of Cyprus: results from two cross sectional studies

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Reviewer: Manuela De Sario

Reviewer's report:

Major compulsory revisions

1) The low response rate in the 2008 survey may have affected the validity of results. Authors discuss possible implications, but, they should substantiate them with more data. For example, which were response rates (and the number of the source population) in rural and urban areas in 2008, and did they differ? Was there any difference between rural and urban areas in how schools were approached to the survey (i.e. Was the school personnel collaborative in data collection in both areas?). Are there any differences in socioeconomic level between urban and rural areas that may have affected parental participation into the survey? May authors provide proxy data (i.e. gender, parental smoking) from a sample of non-respondents in 2008 to ‘estimate’ the magnitude/direction of selection bias? Or, rather, may authors provide a comparison between the population characteristics in the respondents in urban and rural areas and official data sources (i.e. National Statistical Service) with the same aim? Finally, whether there is any reason to suspect that prevalence of parental-reported allergic symptoms differ in respondents and non-respondents should be discussed by authors. For example, the possible higher prevalence of underdiagnosed and uncontrolled asthma in rural areas (see below) may have selectively affected the response to the survey?

2) As authors recognise in the Discussion, there is the potential for uncontrolled confounding due to other population characteristics that may have changed 8 years apart, and socioeconomic variable may play a greater role in my opinion (i.e. parental education, parental employment). Authors are invited to try to quantify the potential bias, i.e. through probabilistic sensitivity analysis (Orsini N, et al. A tool for deterministic and probabilistic sensitivity analysis of epidemiologic studies. The Stata Journal (2008) 8, Number 1, pp. 29–48). Differences in socioeconomic levels can also explain the results about an increase in eczema symptoms only in urban areas, but not in rural areas plausibly more disadvantaged. For example, in Italy, a country ranking similar to Greece in prevalence of atopic eczema in ISAAC Phase I (Williams H, et al. Worldwide variations in the prevalence of symptoms of atopic eczema in the international study of asthma and allergies in children. J Allergy Clin Immunol 1999;103:125-38), the results of the Italian Study of Asthma and Allergies in Childhood suggest a higher prevalence of lifetime atopic eczema in more advantaged families (Bisanti L, et al and SIDRIA-2 Collaborative Group. [Respiratory and allergic disorders in children: differences in socio-economic

3) Studies suggest that in rural areas there is a high prevalence of underdiagnosed and uncontrolled asthma (Perry TT, et al. Underdiagnosed and uncontrolled asthma: findings in rural schoolchildren from the Delta region of Arkansas. Ann Allergy Asthma Immunol. 2008 Oct;101(4):375-81). Authors have data to test differences in symptoms severity (i.e. from number of attacks of wheezing) between rural and urban areas?

4) Different wheezing phenotypes exist during childhood (Martinez FD, et al. Asthma and wheezing in the first six years of life. N Engl J Med 1995;332:133-8). In this regard, authors should test prevalence changes at least stratifying for atopic and non atopic asthma.

5) There is a potential for misclassification of exposure since only current residence was measured. Since the residence is a proxy of the environmental exposures (i.e. farming) and studies have suggested that farming exposure has a differential effect according to the moment of life when exposure occurs (Braun-Fahrlander C. Environmental exposure to endotoxin and its relation to asthma in school-age children. New Engl J Med 2002;347(12): 869-77) authors are invited to discuss this aspect.

6) Why authors have considered a priori family history of atopy as confounder, while it can be an effect modifier? The main changes may have occurred in children without family history of atopy.

Minor essential revisions

1) Were the study areas ISAAC centres, or not? In the latter case, the reasons to adopt ISAAC questionnaire should be provided.

2) The main statistical numbers in the study areas (i.e. number of inhabitants, population density, proportion of children population over the entire population) should be provided and explain the administrative boundary of study districts.

3) Which period of the year survey were performed (i.e. autumn, winter, spring)? Since differences in the period of the survey may have differentially affected symptoms reporting in 2000 and 2008.

4) Throughout the paper, authors should be more rigorous and clear in methods and results description and discussion. For example, authors should better clarify the interpretation of Odds Ratios to assess temporal changes in prevalence.

5) Methods section: study outcomes should be better defined. For example, based on which ISAAC question authors defined “current wheeze”?

6) Authors followed ISAAC questionnaire, but the Greek translation has been found to be problematic (C. Zekveld. The effects of farming and birth order on asthma and allergies. Eur Respir J 2006; 28: 82–88). There are, with little doubt, important cultural and linguistic influences that determine symptom reporting and such background may differ between urban and rural areas. This aspect should be added to the discussion.
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