Author's response to reviews

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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Author's response to reviews: see over
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The Editor, BMC Public Health

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

Dear Editor,

We would like to thank you, Dr De Sario and Dr Anthracopoulos for taking the time to evaluate the above paper. We are grateful for the constructive comments and suggestions of the reviewers which helped further clarify some important issues and improve the paper.

Undoubtedly descriptive in nature, the main purpose of this article was to explore urban-rural differences in the prevalence of asthma and allergies in Cyprus at two different points in time 8 years apart, and as such, explore whether any changes in this period may have been differential in urban and rural areas of the island. We observed that asthma is still on the rise. Furthermore, it seems that most of the changes have occurred outside the main cities so that, unlike a decade ago, there no longer appear to be any marked differences between urban and rural areas. Due to its cross-sectional design, this study is only suited for generating hypotheses about the observed asthma trends on the island. As these changes occurred over such a short period of time, they may reflect the rapid socio-economic, dietary and lifestyle changes rural areas have experienced in recent years.

While the observed rises are consistent with findings from other low-prevalence countries, particularly in the Eastern Mediterranean region (Greece, Turkey, Malta), there are mixed findings in the literature with regards to whether recent rises elsewhere have been more pronounced, or contained, in urban or rural areas. We were happy to see that both reviewers recognised that adding the Cyprus case to the literature will be of interest to your readership.

We have now addressed all the issues and recommendations raised by the reviewers. Below, please find our point-by-point responses as well as relevant action. Corresponding changes are also highlighted in red in the manuscript. We have also made some minor editing changes in the process, which are not highlighted. We look forward to receiving your response.

Yours sincerely,

Dr Ourania Kolokotroni
Reviewer Michael Anthracopoulos:

We certainly agree with the reviewer that parents are increasingly reluctant to offer personal information these days and have now added this comment to the Limitations section of the paper as an additional explanation as to why the participation rate was much lower in the second survey. The reviewer also discusses the need for a separate consent form. It is true that parents who do not wish to participate in a study have the option to simply ignore the questionnaire. However, a separate consent form was required by the Cyprus National Bioethics Committee in order to give approval for the conduction of the study.

Reviewer Manuela De Sario:

Major Compulsory revisions

1. Following the remark of the first reviewer of an increased reluctance to participate in research studies, we share the concerns of Dr De Sario regarding the lower response rate of the 2008 survey. Furthermore, we thank her for pointing out that we had not reported the survey response rate separately in the urban and rural areas. The response rate in 2008 was lower in urban than rural areas (44.5% Vs 59.5%) and we have now added this to the manuscript. The field workers followed a specific protocol that was the same in all regions and hence, this is not a result of any differences in the methodology used or the way schools were approached. We have now presented this matter more thoroughly in the Methodology/Study population and Design section of the manuscript. We agree with Dr De Sario that the low response rate raises concerns about the representativeness of the study population and explored a combination of her suggestions in an attempt to estimate a potential direction of bias of our study population (see Methodology, Results and Limitations section).

(a) In the absence of data on non-responders, we looked though official data sources as well as data from other epidemiological studies in Cyprus. We were successful in tracking down official data on educational attainment by urban and rural residence from the last census. Indeed, the parental level of education in our sample was very comparable with that of people of child bearing age (20-40 years old) as recorded in the last population census. However the latest census performed in 2001 (around the time the first survey took place) is 8 years ahead of the second survey (where the main reason for concern regarding the representativeness of the study sample). Subsequently searching through the literature, we found an epidemiological study on childhood obesity in Cyprus (Savvas SC et al. Prevalence of Socio-demographic associations of undernutrition and obesity in Cyprus. European Journal of Clinical Nutrition 2005) conducted in 2004 with the participation of children aged 2-6 years. We considered this to be a suitable candidate since it captures an age range that would include many of the same children that would have participated four years later at age 8 in our 2008 survey. Parental level of education in that study (with participation rate of 75%) compares very favourably with our study. While in the
published paper, the authors did not include urban Vs rural-specific data on parental education, we gathered this information after personal communication with the first author (Dr S Savva). The information has been summarised in the table below. We also refer to this issue in detail in the Limitations section of the manuscript.

<table>
<thead>
<tr>
<th></th>
<th>Savvas et al sample</th>
<th>Our study population sample</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Urban</td>
</tr>
<tr>
<td>Paternal level of education (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;Elementary</td>
<td>6.3</td>
<td>1.6</td>
</tr>
<tr>
<td>Secondary</td>
<td>50.7</td>
<td>42.1</td>
</tr>
<tr>
<td>&gt;Tertiary</td>
<td>34.4</td>
<td>44.5</td>
</tr>
<tr>
<td>Maternal Level of education (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;Elementary</td>
<td>3.4</td>
<td>0.7</td>
</tr>
<tr>
<td>Secondary</td>
<td>44.6</td>
<td>36.3</td>
</tr>
<tr>
<td>&gt;Tertiary</td>
<td>44.5</td>
<td>52.6</td>
</tr>
</tbody>
</table>

As shown above, there is a close match between level of paternal and maternal education between our population and that in the Savvas et al study; both in terms of overall sample as well as broken down by urban and rural areas using the same classification. A very similar picture was seen with other characteristics such as birth weight (variable divided in 4 categories: <2.5 Kg, 2.5-3 kg, 3-3.5Kg and >3.5 Kg) which was also very comparable between the two survey populations. Although we cannot rule out the possibility of selection bias, we believe that the comparability of our data with Dr Savvas et al in terms of population characteristic such as parental education and birth weight is to a large extent reassuring about the representativeness of our study sample.

(b) In addition, following the reviewer’s helpful direction we performed sensitivity analyses to quantify the potential effect of selection bias on the observed estimates. We used both (i) a probabilistic approach in order to adjust our OR estimates for the change in rural areas between 2000 and 2008, assuming a prior distribution for the bias factor with 95% probability being in the range of 0.6 to 1.7, as well as (ii) a deterministic approach in order to pinpoint to the magnitude of bias factor that would be needed for the urban-rural differences observed in 2008 to overturn (i.e. OR=1) or reach the levels observed in 2000. This has now been described in the Methods, Results as well as Limitations section of the manuscript as appropriate.
2. We fully comprehend the reviewer’s point that socio-economic status is a crucial factor. Whilst socio-economic data were recorded in the 2008 survey, unfortunately, this was not the case in the 2000 survey. As a result, we could not adjust for any changes in the socio-economic status of the children between the two time points. However, we should note that, according to the survey on Income and Living Conditions 2005-2008 (Cyprus Statistical Service) population-level SES indicators have not changed between 2005 and 2008 (e.g. households with an income less than 10,059 Euros per person per year remaining at a constant level of 16% throughout the period). We have now expanded on this issue (Discussion/Temporal changes in asthma and allergy outcomes by urban and rural residence). While no drastic changes in the socio-economic profile of the population have occurred in much of the study period, we recognise that uncontrolled confounding by socio-economic factors might have still contributed to the observed urban-rural patterns. For instance, as the reviewer point out, the higher prevalence of eczema observed in urban areas in 2008 may still be a product of a higher representation of participants of higher socio-economic background in the urban Vs rural sample. Parental level of education was available for our 2008 sample, and we have now explored this issue further in order to see if, and in what way, this affected our urban-rural comparison in 2008. In the absence of a socio-economic classification system in Cyprus, education is the measure most commonly used. Despite the fact that, as expected, a higher proportion of people of tertiary education reside in urban compared to rural areas, this did not seem to affect the direction of the urban-to-rural estimates for any of the outcomes. This is discussed in Discussion/Temporal changes in asthma and allergy outcomes by urban and rural residence.

3. Data on asthma severity were available for participants in both survey years. Asthma severity was defined as: ≥ 4 attacks of wheeze in last 12 months and/or ≥ 1 night per week sleep disturbance and/or wheeze affecting speech in the last 12 months. This also showed to have increased significantly between 2000 and 2008, and the increase was higher in rural than urban areas as was the case with all asthma outcomes. Severity of asthma has been added to the outcome variables (Results and Tables 3 & 4).

4. Following the reviewer’s suggestion, we investigated prevalence changes of atopic and non-atopic asthma (atopic asthma defined as having asthma ever and a family history of atopy) between years 2000 and 2008. We found that 60.9% of children that reported ever having asthma had atopic disease whilst the equivalent figure in 2008 was 59.2% (i.e. amongst ever asthmatics the proportion of those with atopic disease did not change significantly between the two points in time). Furthermore, as described further down (point 6), changes in asthma and allergy prevalence have not occurred differentially in children with and without family history of allergies.

5. We agree with the point that early life exposures are important in asthma and allergy development. Information on the place of residence (and therefore, classification into urban vs. rural) in our study was restricted to one point in time. As the reviewer suggests, this might
have introduced misclassification of exposure, in the sense that children residing in rural areas at the point of survey may have not grown up in those areas (and may have even moved there at some point in their lives from urban areas). Limited by its cross-sectional design with two different sample of children at age 8 a decade apart, the purpose of this study was not to investigate whether a rural environment (and which aspects of it) pose an independent effect on the study outcomes but to describe whether previously recorded differences between “who lives” in urban Vs rural areas on the island are still strong – in essence an assessment of current patterns and not an investigation into the effect of rurality as an “exposure”. In any case though, Cyprus, unlike many European countries, appears to have a very low population mobility, particularly once people start a family. Population mobility (as recorded in the last census in Cyprus and defined as moving to a different address within a year from the census) is as low as 0.8%. Furthermore, census statistics show that at age 0-4, internal migrants were 10 per 1000 i.e. 1 in 100 children moved to a different area of residence within one year. Therefore, even if it is not in the aims of the study, it wouldn’t be far fetched to suggest that in this case the urban Vs rural exposure of children at age 8 (as collected in the survey) is highly likely to also represent the early life exposure of the child. We have now discussed this issue at length in the Discussion/Temporal changes in asthma and allergy outcomes by urban and rural residence section of the paper.

6. Since family history of allergies (FHA) is a strong predictor for the presence of asthma and allergies, we had to include it in the models to control for any confounding it may pose in the observed urban-rural differences. As we explain in the Limitations section of the paper, we found that participants who live in rural areas reported consistently lower frequency of FHA than those living in urban areas both in 2000 and in 2008 (see Table 2). The observed increase in the reporting of family history of atopy in both urban and rural areas between the two surveys may represent a “real” change or may simply be the result of sampling. As we now mention in Results/Temporal changes in prevalence between years 2000 and 2008, we have checked for effect modification of FHA and found no statistical evidence that the magnitude of the effect was different in children with and without FHA for any of the study outcomes.

Minor Essential revisions

1. The study areas have not been registered as ISAAC centres. However, the ISAAC questionnaire was adopted, not only because it is a reliable and widely used tool for the purpose of assessing asthma and allergy symptoms, but mainly to enable us to make comparisons – both internal (since this was also the tool used in the original 2000 study) as well as with other countries within and beyond the Eastern Mediterranean region. This is further clarified in the section Methodology/Study questionnaire.

2. Information regarding the number of communities/municipalities, number of inhabitants and population density in the urban and rural areas of the Nicosia and Limassol Districts has now been added to the section Methodology/Study questionnaire.
3. The survey was conducted during the course of the academic year starting in October and ending in March in both study years 1999-2000 and 2007-8. Therefore we believe that in this way we have minimized any bias that could have differentially affected symptom reporting had data been collected during different periods in the two survey years. We have now provided this information in the paper in the section Methodology/Study population and design.

4. Logistic regression models were used in order to assess temporal changes in prevalence of study outcomes, while controlling for possible confounding due to differences in the composition of study 2000 and 2008 samples. This has now been better explained in the relevant section (Methodology/Statistical Analysis) as well as a clearer interpretation of the Odds ratios has now been provided, at parts, in the Results section.

5. The definition of all study outcomes has now been provided in the section Methodology/Definition of study outcomes and severity of asthma has also been added.

6. We agree with the point that cultural and linguistic differences are certainly important in determining symptom reporting across the world. The reasons why the ISAAC questionnaire was adopted in the study were explained above. The Greek translation we used in this study is currently the only available Greek version of the ISAAC core questionnaire which has been adopted by the ISAAC study and was used by two ISAAC centers in Greece (Athens, Thessaloniki). We believe that due to the fact that the level of education amongst parents of young children in Cyprus is high both in urban and rural areas (i.e. only 0.6% and 2.7% of parents with elementary education in urban and rural areas respectively), any linguistic/cultural influences that could have affected symptom reporting should be minimal. In addition, a number of research studies in Greece including the PANACEA epidemiological study have used the same version (Priftis KN, Panagiotiakos DB, Anthracopoulos MB, Papadimitriou A, Nicolaidou P. Aims, methods and preliminary findings of the Physical Activity and Allergies in Children Examined in Athens (PANACEA) epidemiological study. BMC Public Health 2007; 7: 140-6). In another study aiming to assess differences in asthma and atopy between the two major cities in Greece, Athens and Thessaloniki (arguably, also populations with cultural differences and, in fact, geographically far more distant from each other than the areas approached in the island of Cyprus) the Greek version of the ISAAC questionnaire was adopted. The study assessed symptom reporting but also objective measures of allergy (skin prick testing). The results indicated that the prevalence of asthma and allergy was higher in Thessaloniki than in Athens and symptom reporting was consistent with a higher prevalence in atopic sensitization (Papadopoulou A et al. Comparison in asthma and allergy prevalence in the two major cities in Greece: the ISAAC phase II survey. Allergol Immunopath, 2011).