Author's response to reviews

Title: Prevalence of asthma and allergies in children from the Greek-Cypriot and Turkish-Cypriot communities in Cyprus: a bi-communal cross-sectional study.

Authors:

Demetris Lamnisos (demetris.lamnisos@cut.ac.cy)
Maria Moustaki (mar.moustaki@gmail.com)
Ourania Kolokotroni (ourania.kolokotroni@cut.ac.cy)
Huseyin Koksoy (hkoksoy@yahoo.com)
Muharrem Faiz (kadem@mycyprus.net)
Kenan Arifoglu (karifoglu@yahoo.com)
Donald K Milton (dmilton@umd.edu)
Nicos Middleton (nicos.middleton@cut.ac.cy)
Panayiotis K Yiallouros (p.yiallouros@cut.ac.cy)

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Author's response to reviews: see over
20 May 2013

Dr. Isabella Annesi-Maesano,
Associate Editor
BMC Public Health

Dear Dr Annesi-Maesano,

Re: Manuscript MS: 1199178007804063 entitled "Prevalence of asthma and allergies in children from the Greek-Cypriot and Turkish-Cypriot communities in Cyprus: a bicommunal cross-sectional study." : Point-by point reply to reviewer’s comments

We would like to thank you and the reviewers for evaluating the revised version of the above manuscript. We are grateful for the comments of Dr Bulent Karadag and Dr Alejandro Videla. We have now addressed the few remaining points raised by Dr Alejandro Videla.

Below, you will find a point-by-point response along with the relevant action. Any additional changes to the manuscript as a result of this second revision are highlighted in blue while changes as a result of the previous round of revision are shown in yellow. We thank you for offering us the opportunity to resubmit a revised version and look forward to receiving your response.

Yours sincerely,

Panayiotis Yiallouros, MD PHD
Point–by point response to the comments of Dr Alejandro Videla

Major compulsory reviews

1) Abstract:
The phrase “Controlling for risk factors” should be replaced with a phrase commenting only the differences that remained significant in the adjusted analysis. The phrases referring that the pattern remained higher for a group can only be applied to adjusted analysis. If the OR were higher for a group but the difference did not show statistical significance, the purpose of the statistical adjustment is lost.

Reply: We agree with the Reviewer that in our effort to keep the abstract short we may have simplified and over-generalized our conclusions with regards to the adjusted analyses. Differences between the two communities in terms of the prevalence of current rhinoconjunctivitis and current wheeze (at least in the younger age-group) remain statistically significant after controlling for risk factors. We have now made the following changes: “Controlling for risk factors did not account for the observed lower prevalence of current rhinoconjunctivitis (in either age-group) and wheeze (at least in the younger age-group) among G/C children while differences in the prevalence of eczema between the two communities were no longer statistically significant”.

2) The last phrase is not clear. The message so far had been that the presence of risk factors was more frequent in the G/C community but against published literature this community had a lower prevalence of respiratory outcomes. I think a possible rephrase could be: “Even as risk factors were not clearly more frequent in any community, the G/C children had more risk factors and had a lower prevalence of asthma and allergies.”

Reply: We had originally hypothesized that the prevalence of asthma and allergies would be lower among G/C children, mainly due to the presumably less “westernized” way of life in the T/C community. Indeed several “hygiene hypothesis”-related risk factors such as bedroom sharing, a less urbanized environment and exposure to farm animals (but not early nursery attendance) were indeed more prevalent in the T/C community. However, exposure to tobacco smoke was also more prevalent in this community, producing a mixed picture where it is difficult to quantify which community had more risk factors than the other. Of course the most notable result was that the prevalence of asthma and allergies was lower among G/C children even though family history of allergy appeared far more prevalent in this community.

We agree with the Reviewer that while these complex results are presented in detail in the manuscript, the message might not effectively come forward in the conclusions in the abstract. In order to better but succinctly convey this message, we have now rephrased the conclusions of the abstract accordingly: “A mixed picture of potential risk factors was observed in the two communities of Cyprus, not consistently favoring one over the other community since, for example, bedroom sharing and rural living but also exposure to tobacco smoke were more common among T/C children. Risk factors investigated here do not fully account for the lower prevalence of asthma and allergies among G/C children, especially against a background of higher family history of allergy in this community.”
3) Prevalence of asthma and allergic symptoms in the G/C and T/C communities:

Correct multivariate for multivariable

Reply: Indeed, we agree with the Reviewer that there is some confusion in the literature with regards to the use of the terms “multivariate” and “multivariable”. Frequently, both terms are used even interchangeably to refer to the results of multiple regression models. However, we agree with Kirkwood and Sterne. *Essential Medical Statistics*. 2nd Ed. Chapter 11: Multiple Regression, pp. 106 that: “In the strict statistical sense, multivariate analysis means the study of how several outcome variables vary together” i.e. methods such as factor analysis and cluster analysis. According to the same source “A better term for such model [multiple regression models] is to call them multivariable regression models.” Hence, we prefer to use the term multivariable throughout the manuscript.

4) The part stating that the ORs did not change their pattern but lost significance in adjusted analysis should be rephrased. i.e: “After controlling for participants’ characteristics in multivariate models, prevalence ratios were different for …… . Associations for……did not show statistical significance”.

Reply: We have now followed the Reviewer’s suggestion to re-write this part so that it refers specifically to the adjusted estimates that remain statistically significant as well as pointing out the ones that are no longer statistically significant. Specifically, the sentence now reads: “After controlling for participants' characteristics in multivariable models, there was only slight attenuation in the estimates. However, while adjusted Odds Ratios (aORs) were lower than 1 for all outcomes, only current wheeze in the younger age-group (aOR 0.73, CI: 0.54-0.98) and severe asthma in the older age-group (aOR 0.52, CI: 0.34-0.85) remained statistically significant. Adjusted ORs for severe asthma in the younger age-group and current wheeze in the older age-group were no longer statistically significant at the 5% level.”

5) “After repeating” should be rephrased as “In a subgroup analysis of children from both parents of Cypriot the results remained largely unchanged (Table 3). The prevalence in the T/C decreased for all study outcomes…”

Reply: Following the Reviewer’s suggestion the sentence now reads: “In a subgroup analysis of children whose parents are both of Cypriot origin (i.e. either both G/C or both T/C in each community respectively), the results remain largely unchanged (see Table 3). However, the prevalence estimates in the T/C community decreased for all study outcomes, and as a result the gap between the two communities appeared smaller”.

Minor essential revisions

The paper needs extensive English editing, I have noted some corrections but I think the writing style should be edited to obtain a more concise and clearer phrasing. I am presenting alternatives in several cases to guide the authors. Maybe a correction by an English native speaker could be useful.

Reply: We thank the Reviewer for taking the time to produce a comprehensive list of suggested linguistic changes. We have now carefully looked though all the suggestions which have now been
incorporated in the manuscript. In the process, we have also edited the rest of the manuscript and as a result, there have been some additional minor editing changes, which are also highlighted.

Abstract:

Aim: To estimate the prevalence among…
Reply: This has been done.

Methods: 13-14 years. Relative differences…
Reply: This has been done.

Results:
among children in the G/C compared with the T/C community.
Reply: This phrase now reads “among G/C compared to T/C children in both age-groups”

Surprinsingly, the proportion reporting family history of allergy almost doubled among the G/C group.
Reply: This sentence now reads “Surprisingly, the proportion reporting family history of allergy was almost double in the G/C community.”

Controlling for risk factors did not modify
Reply: This sentence has changed as a result of the reviewer’s suggestion (see point 1 above) and now reads “Controlling for risk factor did not account…”

Background:

“A characteristic example…” I believe a clearer version could be “In Germany, the population of West Germany presented a 150% increase of prevalence in the pre-unification period while the East Germany population had a marginal increase in the same period. The difference narrowed gradually after re-unification”
Reply: This sentence now reads “The most characteristic example is that of West and East Germany before unification. Compared to the 150% increase recorded in West Germany over the pre-unification period, the increase in East Germany during the same period was only marginal. The difference gradually narrowed after re-unification.”

“…were recently reported to be rising”
Reply: “to be on the rise” has been replaced with “to be rising”

Definition of outcome variables:

“The Turkish version was tested ….parents and found to be concordant”
Reply: This has now changed to “The Turkish version of the ISAAC questionnaire was tested in a pilot study conducted three months before the ISAAC study. The parental self-administered questionnaire and face-to-face interview with parents were found to be concordant.”

Definition of predictor variables:
“animals kept in the household”
Reply: “animals that are kept in the household or yard” has been replaced with “animals kept in the household or yard”

Population characteristics:

“While many presumably protective factors as per the hygiene hypothesis”
Reply: This has been done.

Prevalence of asthma and allergic symptoms in the G/C and T/C communities:

“Lower prevalence was observed for all respiratory outcomes”
Reply: This has been done

“...a slightly higher prevalence of current eczema symptoms was found among”
Reply: “was recorded” was replaced with “was found”

“Despite the much lower...” this phrase is too long and should be shortened into several parases.
Reply: Indeed this paragraph was previously too long and it has now been broken into two sentences.

Association of asthma and allergic symptoms with predictors involved in the hygiene hypothesis:

“suggest a protective effect absent in the older age-group”
Reply: This phrase has now been broken in two distinct sentences and it now reads “adjusted ORs for current wheeze (aOR: 0.72, 95% CI: 0.53, 0.98), severe asthma (aOR: 0.56, 95% CI: 0.56, 0.91) and current eczema (aOR:0.36, 95% CI: 0.20, 0.61) among children aged 7-8 years with two or more older siblings suggested a protective effect. Nevertheless, this was not generally the case with the older age-group.”

“While no overall effect was observed in this group, there was some evidence...”
Reply: “While an overall effect was not observed” has been replaced with “While no overall effect was observed”

“the association with maternal smoking during pregnancy is restricted to the T/C group..”
Reply: 
Reply: “is mainly driven” has been replaced by “is restricted”

Discussion:

“Refuting our original hypothesis”
Reply: “To refute” has been replaced by “Refuting”.

“allergies was found”
Reply: The phrase “was recorded” has been replaced by “was found”
“increased risk of allergies in the children”
Reply: This sentence now reads: “suggesting a paradox of a community with lower prevalence of family history of allergy among parents but increased risk of allergies among children”.

“It is likely that allergic diseases were underdiagnosed in”
Reply: The sentence now reads “It is likely that allergic diseases were underdiagnosed among family members of the T/C participants.”

“This may be a consequence of less access of the previous generation of T/C to specialized primary care and therefore less detection of disease or alternatively the result of using other diagnostic terms…”
Reply: The sentence now reads “Perhaps, this may be the consequence of lower access of the previous generation of T/C to specialized primary care and, as a result, under-detection of allergic diseases or, alternatively, it may be the result of using other diagnostic terms for asthma, eczema or rhinoconjunctivitis in the T/C community at the time”.

“Eczema was more frequent in the G/C community, differing from the prevalence trend of…”
Reply: Rephased: “In contrast to the pattern observed in the case of asthma and hay fever, eczema was more frequent in the G/C community”.

“Probably genetic susceptibility or unknown environmental risk factors might reinforce (?) the…”
Reply: We rephrased the sentence to make the meaning clearer but we feel the verb “underlie” is more appropriate than “reinforce” since we refer to factors that may “be the cause of” the observed differences.

Omit “there are discussed below in turn”
Reply: This phrase is now omitted.

“…increased the risk by 40%”
Reply: This has been done.

“a significant risk of wheezing with exposure to tobacco smoke”
Reply: This has been done.

Conclusions

“…reinforced this difference”
Reply: The sentence has been replaced with “The extent to which genetic susceptibility or other environmental factors not accounted for in this study account for the observed differences is not known”.
