Letters to editor

Clinical differences between children with asthma and rhinitis in rural and urban areas

Diferencias clínicas entre niños con asma y rinitis de áreas rurales y urbanas

Dear editors, cordial greetings

In their article, Sánchez, *et al* [1] have reported about an interesting study on asthma and rhinitis symptoms among children in urban and rural Colombian areas, describing that the control of symptoms, over time, is more difficult among children in urban areas. Their article has the methodological advantage of having done a prospective follow-up of pediatric patients with asthma and rhinitis; nevertheless I have some questions:

1) The sample size calculation is not clear. The authors mentioned the prevalence of asthma and rhinitis in the urban areas and their corresponding error, but they did not use these parameters in the sample size calculation. On the other hand, the authors argued that the main outcome was comparing the treatment of asthma and rhinitis between urban and rural areas; thus readers could assume that the measure of effect was the difference of the Asthma Control Test (ACT) score between both areas; but the authors did not clearly explain it. Furthermore, it is not clear why the ratio of urban/rural subjects is 1.57; is the ratio observed in the study health centers? In this line, it seems that the appropriate sample size calculation must have been the difference of means between two independent populations, although the authors did not report any ACT effect size based on previous studies. Thus, I have estimated the means difference (as the effect size) given the power (80%) and the study sample size (urban= 201 and rural= 128) provided by the authors; using Stata® 14.2 (*power twomeans* command). In this manner, the detectable effect size would be 3.5; which is higher than the ACT effect size estimated in the Sánchez, Sánchez and Cardona's article (i.e.: 3.0), leading to an underpowered study, at least for the cross-sectional estimates. In this manner, what was the appropriate sample size calculation?

2) The research was designed as a follow-up study with four assessments, at 3, 6, 9 and 12 months, but the statistical analyses were done using a cross-sectional approach at each measurement without taking into account the multilevel nature of the repeated (or longitudinal) measures of each patient and without the baseline adjustments of the outcome scores. The cross-sectional analyses are not appropriate for determining within-subject's longitudinal patterns; for example, Figure 1 shows the hypothetical follow-up of a health symptoms score of five subjects, with two assessments over

time (T=1 and T=2). The estimated cross-sectional mean at each time is the same (24 points), but individual persons' trajectories (i.e. the lines) show different patterns: some subjects improve and others worsen over time. In this manner, it is important to emphasize that in the Sánchez, Sánchez and Cardona's article, the monthly measures of each single patient are nested (or clustered) into each individual, which constitutes a longitudinal multilevel structure [2]. Nowadays, there are several parametric and non-parametric statistical approaches for dealing appropriately with this kind of longitudinal data analysis: i.e. follow-up of patients with repeated measures of the outcome variables over time [3,4]. The current longitudinal data analyses techniques have the advantage of allowing for the analyses of incomplete and unbalanced longitudinal data: i.e. data with missing measurements (under the MCAR or MAR missing data assumptions), attrition and/ or different assessment moments [5,6]. Furthermore, nowadays these longitudinal data analysis, with mixed regression models or Bayesian approaches, have been implemented in several statistical software packages[4]. These techniques allow dealing not only with normal continuous outcomes, but also with non-normal continuous, dichotomous and polytomous categorical outcome variables [6]. Furthermore, in Sánchez, et al. [1], Figure 3, the 12-months pharmacotherapy comparisons between urban and rural children did not adjust for the baseline values of the corresponding pharmacotherapy scores, which were different between urban and rural children. Thus, the estimated differences at the 12-months follow-up could be explained, instead, by those baseline scores. Finally, due to the research design is an epidemiological observational study, it is necessary to perform analyses adjusting for the confounding variables which are conceptually related with the outcome variables [7,8], because children's urban or rural residences were not randomly allocated. In this manner, what are the effects of the urban environment on the pharmacotherapy scores and the symptoms of asthma and rhinitis over time, after performing the appropriate statistical analyses (i.e. multiple and repeated measures [3,4] regression models)?

3) When the design of a research is a longitudinal study with repeated measures, and its data are appropriately analyzed with up-to-date statistical methods, this situation allows dealing with smaller sample size given the efficiency of the longitudinal data analysis methods, which improves when adding more measurements per subject [4]. Sample size calculation guidelines, for studies with repeated measures, have been addressed by Guo, Logan, Glueck and Muller [9]. Did you take into account these sample size calculations in your study?
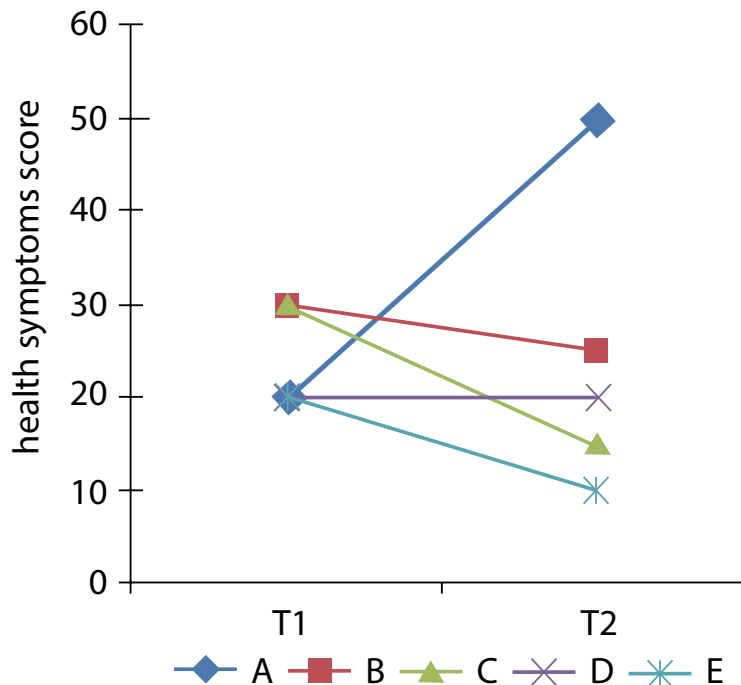
Figure 1. Hypothetical follow-up of a health symptoms score of five subjects

4) Neither the location nor the health care level of the study centers are clear; nor are the criteria to select them. For example, if children of rural areas with the worst symptoms levels are referred to higher complexity health centers different to those in the study, it could be a selection bias which could affect the study findings[7,10]. Thus, which are the health care levels and locations of the study centers and which are the related potential biases?

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Authors Response: Clinical differences between children with asthma and rhinitis in rural and urban areas

Dear Editors:

We greatly appreciate the interest shown in the article «Clinical differences between children with asthma and rhinitis in rural and urban areas», which we hope will be one of several future articles that we intend to carry out in the study cohort. To the questions generated by the reader, one is focused on the calculation of the sample size, while the other two questions are focus in the method of analysis, and the reader suggests, it could be more robust.

Regarding the sample size, we describe that infant asthma in urban areas of Medellin was 11% and rhinitis 23%, according to previous studies. There is no data available for the rural area. We note that with a confidence level of 95%, a power of 80% and a sample size error of 0.5%, the sample size was calculated; estimating 201 children for the urban area and 128 for the rural area. Finally, we recruited and were able to continue for a year, a total of 248 children from the urban area and 134 from the rural area. The complaint of the reader, is focus that the more appropriated

technique would be «… *the appropriate sample size calculation must have been the difference of means between two independent populations, although the authors did not report any ACT effect size based on previous studies*.» First, we fully agree with the reader that for this type of design, the study lost power by the form of sample size calculation. We did not find studies with the urban and rural ACT tests in the studied population, which made it impossible to obtain these parameters to perform the sample size calculation by the technique «power two means» (difference of means of two independent groups).). As we noted in the article, we do not have previous data in the rural population that allow us to infer the precise prevalence of asthma in this area; as we also noted in the article the prevalence in Colombia of asthma in the general urban population is 11%, there are also data that indicate that in the child population (less than 12 years) it is around 23%; if we work with these two prevalence where we assume that the highest in children is for the urban population and that possibly the lowest corresponds to what happens in the rural population [1] and assuming the parameters; alpha 0.05, power 0.80, delta 0.12 rural prevalence 0.11 vs. urban prevalence 0.23, a sample size of 306 is required; 153 for each group; in the urban area we had the availability of 201 children and in the rural area we made 128, which is close to the desired. Therefore we consider that we fulfill the expectation according to the mathematical formula used (chi-squared test comparing two independent proportions).

Regarding the following two questions of the reader that are focus in the design of the study and the analysis of the data; it is important to clarify that although a follow-up was carried out over time, for this study we wanted to focus in compared two groups (rural and urban) specially after 12 months of clinical treatment. We agree with the reader that a longitudinal analysis of repetitive measures would be appropriate and would provide additional interesting information for the effect of changes in the tests over time (e.g. ACT), however, for this study, we wanted to focus the

results and the discussion, in compare these measures in two moments clinically relevant for the doctor; In the first consultation, the doctor sends a treatment and in the follow-up can make adjustments according to the clinical response; usually after one year if patient have a good clinical control, begins the process of dismantling the therapies. That's why we preferred to highlight the final moment versus the initial moment. We recognized that the information in the intermediate times (3 months and 6 months) could be analyze in a longitudinal way, and in this form, we could evaluate the effect, but it contributes less for the objective that we planted, that was to compare if there were differences in the groups studied, especially at the end of the study, presumably due to the medical interventions carried out.

Again, we thank the reader for their pertinent suggestions that put in their real dimension the results of our research and that will serve us for the next analyzes that we will carry out with this population.

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