Subject: Vitamin C and astma - paper
From: Harri Hemila <harri.hemila@helsinki.fi>
Date: 7.12.2011 17:35
To: Jan Lötvall <jan.lotvall@gu.se>
CC: Mohammed Al-Biltagi <mbelrem@hotmail.com>

Dear Dr. Lötval,

Our paper on vitamin C and asthma was published last summer in Clinical and Translational Allergy.

I was particularly proud of that paper and I was very gland when you accepted our paper to CTA.
The modification of vitamin C effect by age and other factors is a novel finding, vitamin C is cheap and safe, and asthma is a common disease...

However, now I found that the Egyptian data on which my analysis was based on is flawed.
First, I will briefly describe the background of the paper, and then I will describe how I found the problems and what they are.

I have a long lasting interest in vitamin C. I am the first author of Cochrane reviews on vitamin C and the common cold and on vitamin C and pneumonia. In the former, based on five RCTs, we show e.g. that vitamin C decreases the incidence of colds in persons under heavy acute physical stress by 50%.
In the pneumonia review, we found 3 prophylactic trials and in each of them vitamin C group had 80% or greater decrease in the incidence of pneumonia. However, these 3 pneumonia trials were carried out under special conditions, for example, one was carried out in the UK in the 1940s and dietary vitamin C intake was particularly low. There is no basis to assume similar effects for ordinary people in the western countries, yet on the basis of my work it seems possible that vitamin C may have effects e.g. in developing countries and on people under heavy physical stress.
In addition, there is one RCT in Nigeria (1980) in which 22 asthma patients in vitamin C group had 9 asthma attacks and 19 asthma patients in placebo group had 35 asthma attacks during the trial, corresponding to RR=0.22.
Thus, there seem to be some situations when vitamin C may be involved in diseases other than scurvy.

In 2009, I wrote a criticism against the Cochrane review on vitamin C and asthma. I pointed out that there were lots of errors in that review.
The published version of my critique is available at my home page:
http://www.ltdk.helsinki.fi/users/hemila/CA/HH_2010_L_CochraneAsthma.pdf
When I submitted that criticism, my goal was to kick the authors to correct their errors and make a better version.
However, the managing editor wrote back to me that there was no one in charge of that review (Cochrane reviews are intended to be updated regularly and there should be someone in charge!). He asked whether I would like to take charge of that review. I was puzzled but promised to take charge and started to search the literature systematically and write a fully revised version of the Cochrane review (currently at reviewers).
In my searches, I found a new trial by Biltagi et al. which was published in Acta Pediatrica (2009). Methodologically that was a good trial, and the results were dramatic so that vitamin C decreased symptoms and increased FEV1 values.
I sent Dr. Biltagi an email in which I asked whether it might be possible for me to have the C-ACT and FEV1 data so that I could re-calculate myself the means and SD:s.
I received the data and calculated appropriate values for my Cochrane review.

While I was continuing my work on the Cochrane review on vitamin C and asthma, I started to think that I could carry out a much better statistical analysis of the Egyptian data than the version published in Acta Pediatrica (2009), and I could write a much better discussion since I know the literature on vitamin C very well.
I contacted Dr. Biltagi again and suggested collaboration so that I would carry out a more sophisticated statistical analysis of their data and he accepted.
I wrote a protocol for the subgroup analysis and when we were satisfied with the protocol, he sent the vitamin C data to me and I carried out the statistical analysis.

While I was working on the manuscript, I wrote an email in which I explicitly asked Dr. Biltagi to check the most essential parts of the data that I had at my hands against the original experimental data (email Dec 17, 2010 see attachment). Dr. Biltagi replied Dec 23 “Dear Prof. Harri. I revised the data that you want to be revised according to the original excell file and I found that all the data you entered are correct.”
Although it was not clear from that reply whether he checked the data against the original experimental data as I had asked, I took that reply as Dr. Biltagi taking responsibility of the validity of the data that I had at my hands.
Furthermore, the 2009 paper had 5 authors and I implicitly assumed that such a group divides responsibilities so that someone had charge for checking that the EXCEL file was consistent with the authentic experimental data.

I take full responsibility of the statistical analysis of the data that I received. However, I have not visited Egypt to check the data that I had at my hands against the original experimental data.
That vitamin C project ended by our study being published in CTA.

Since Dr. Biltagi also had a zinc phase in their 2009 trial, I suggested that we should carry out a more detailed analysis of the zinc effect in the same way as we analyzed the vitamin C effect.
I wrote a protocol and when that was ready, Dr. Biltagi sent me the zinc data (Nov 7, 2011).
Last Wednesday (Nov 30, 2011) I started the analysis of the subgroup differences in the zinc effect.

There were no subgroup differences for C-ACT, but age modified the effect of zinc on FEV1. No other subgroup variable modified the effect on FEV1.
Therefore, I reasoned that I could make an x-y plot of the relationship between age and the effect of zinc. Figure is an effective way to show the relationship between two variables.

I had a problem with the figure, so that only half of the data points could be seen. Of course, one or two data points can be overlapping when there are 60 observations. However, it is not possible that half of 60 data points are overlapping so closely that they cannot be seen.
Obviously, I was confused with this problem and, using EXCEL, I sorted the data simultaneously by age and by the effect of zinc so that the effect of zinc can be compared for children with the same age.
In this reordering, I found that the data is paired so that two children with the same age both have the same FEV1 value after zinc administration. Obviously, I understood that this might be the case also for the vitamin C data which was the basis for our study published in CTA.
I combined the earlier vitamin C data with the new zinc data, and both FEV1 and C-ACT measurements are paired for both vitamin C and zinc phases (see file: Comparison of FEV1 values ordered...).
I also found that C-ACT data for vitamin C and zinc phases is paired (see file: Comparison of C-ACT values ordered...)
However, not all data was paired. The children pair with the same age and the same effect on FEV1 and C-ACT had different gender, weight and height (see file: Comparison of FEV1 values ordered...).

Then I wondered where this pairing comes from.
I found that 30 lower observations in the original EXCEL sheets I received are identical with the 30 top observations in the EXCEL sheets, for both zinc and vitamin C data and for C-ACT and FEV1 (see file: Zinc data..).
The vitamin C laboratory data that I received one year ago is also duplicated similarly except in some limited parts (see file: Biltagi_Lab_Duplicates). The means and SD:s of the lab values are the same as those in the Acta Pediatrica paper (2009), as are the means and SD:s of the clinical outcomes that I have analyzed.

When I found the pairing problem last Wednesday (Nov 30), I wrote to Dr. Biltagi the same day and informed him about the problem and asked for explanations.

Dec 4, I received an email in which Dr. Biltagi attached an explanation from their IT department, which does not help me to understand how the duplication has originated (I am forwarding that email after this email).

In that mail, Dr. Biltagi suggested that I might carry out statistical analysis with

one half of the data, removing the duplicates.
When there is duplication of data, the estimates for the 60 observations are the same as the estimates for the upper 30 observations, but the confidence intervals (CI) for the 30 pairs (i.e. 60) are narrower than the CI:s for the 30 single observations. This comes directly from basic statistics.
If there is no systematic difference between the upper 30 observations (assuming them correct) and the - real (unknown) - lower 30 participants, then the real estimates and confidence intervals do not necessarily differ much from those published.
Also, this pairing problem does not necessarily invalidate the modification of vitamin C effect by the identified variables.
Although such speculation is sound, firm answers require the authentic data for the 60 participants.

In any case, this pairing problem invalidates every single figure in my Tables 2 to 7.

I have some 50 original papers, I have read many reviews of my own manuscripts, and I have written lots of manuscript reviews myself.
I have been very careful with my own tables so that I have checked them several times before submitting the manuscript.
And, when I have got the proofs, I have carefully re-checked the figures also in the proofs. In some cases I have found errors in proofs (mainly minor, mainly in decimal points), but I have never found errors in my published papers and no-one has suggested that some of my published results might be unreliable.
My Cochrane review on vitamin C and the common cold is among the most read Cochrane reviews and therefore there is quite much feedback. Most of the feedback argues that I am not positive enough about vitamin C. There are also 2 comments by statisticians who suggested some improvements, yet those issues had no influence on the calculated estimates or conclusions.

It was a nightmare to realize that all figures in Tables 2 to 7 are incorrect.

Thus, how should we go forward?
Starting to see the nightmare, my first thought was to retract our paper.
However, when I slept over a few nights, and when Dr. Biltagi describes that he has the original data at his home and he will do his best to prepare a new EXCEL file in which all data is corrected, checked and re-checked (I am forwarding two of his most recent emails after my own mail: Dec 4 and Dec 5), and based on the statistical reasoning described above (perhaps there are not very dramatic differences), then I thought that we might publish an Erratum which gives the corrected values for Tables 2 to 7.
If the correct figures do not change much from those published, then the discussion and conclusions do not change at all. If that turns out to be the case, the Erratum would be lengthy as it would contain 6 tables, but the old text would still be fine.
On the other hand, if the real results turn out to be fundamentally different from those published, then we have a serious problem.
We cannot know which of these two alternatives is true, until I have the corrected EXCEL file for analysis.

The editor of Acta Pediatrica also needs to be informed about this pairing problem, because the problem invalidates the figures of the 2009 paper.
But I will first ask your opinion on how we should proceed with the CTA paper.

Thus, is it OK that we wait for Dr. Biltagi to prepare a new version of the EXCEL file for the new statistical analysis and only then decide what to do with the paper? How do you recommend we should proceed?

Yours sincerely,

Harri Hemilä
Helsinki, Finland

Attachments:

Email_2010_12_17.pdf	11.2 KB
Zinc data_2011_11_07_short.xls	17.5 KB

Biltagi_vitC_Lab_Duplicates_111203.xls	72.0 KB
Comparison of CACT values_ordered_2011_12_07.xls	154 KB
Comparison of FEV1 values_ordered_2011_12_07.xls	31.0 KB