Title: Population-based analysis of non-steroidal anti-inflammatory drug use among children in four European countries. What size of data platforms and which study designs do we need to assess safety issues? The SOS project

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Author's response to reviews: see over
Dear Dr Chiappini,

Thank you for your time in assessing our work and for giving us the chance to revise our manuscript. The revised manuscript has been submitted through the BMC web site.

We would like to thank the reviewers for their welcome advice and positive comments. Please find below our point-by-point response to each reviewer’s report. We hope that this is satisfactory.

All changes in the revised manuscript are described below except for the following changes which are not related to the reviewers’ reports. First, according to a change in name of the respective department at University of Milano-Bicocca, we changed affiliation number five. Second, we corrected a typing error in Figure 1. For the upper-right panel of Figure 1, it now reads “Prevalence rate by calendar month (per 1000 person-months)” instead of “Prevalence rate by calendar month (per 1000 person-years)”.

Yours sincerely,

On behalf of the co-authors,

René Schade
Referee 1, Joseph A Delaney:

This report is an interesting exploration of the issues of statistical power in the SOS project seeking to look at the safety of NSAID class medications in children. These databases are European and cover nearly 8 million children and adolescents. The report is well written by thoughtful scientists who have carefully thought through some key methodological issues.

Discretionary Revisions

1. With roughly 70% of the exposure being to ibuprofen (making it the clear drug of choice) and it being an OTC medication, would not the primary contrast for comparative safety be ibuprofen versus not ibuprofen? It would be useful to see how the power in table 3 looked for non-ibuprofen NSAIDs.

Answer: We agree with the reviewer that power calculations for non-ibuprofen NSAIDs can provide useful information with respect to comparative safety studies where ibuprofen would be the primary exposure of interest. In our revised manuscript, Table 3 now contains a row showing the result of the power calculation for non-ibuprofen NSAIDs.

2. Was there any way to determine a dose-response element for ibuprofen or was sample size and/or data capture inadequate.

Answer: As referred to by the reviewer, data capture in terms of prescribed NSAID dose was not adequate for all databases. Among the seven databases in the SOS project, only IPCI, THIN, PHARMO, and Pedianet have captured adequate information on prescribed daily dose. The dose response may be modeled in the case-control studies of the SOS project for those databases with adequate information on dose regimen. For this manuscript, the analysis does not consider dose because this drug utilization study considers factors for which data capture was similar across all databases such as age, sex, and calendar time.

3. The suggestion that a case-only design would make sense is interesting and, I believe, correct. However, would the self-controlled case series design be appropriate or would post-event exposure time be different than pre-event exposure time? Would any of the events be fatal? These are tricky issues with the SCCS (which is the gold standard in the world of vaccines) that might be considered (I think that there are advanced versions of the SCCS that can handle these issues but it might be useful to get a data driven insight). Similarly, would a case-crossover approach make sense or could there be secular trends in prescribing of NSAIDs that would make a case-time-control design appropriate. These sorts of questions naturally arise from a read of the discussion and it would increase the impact of the paper to provide some guidance on these issues in the context of European prescribing databases.

Answer: We thank the reviewer for his positive comment and acknowledge his competent grasp of case-only study designs. Referring to the reviewer’s questions, indeed, for several pediatric outcomes of interest, post-event probability of NSAID exposure would be different from that during pre-event time. To delve into details of epidemiological study designs is not the primary focus of this manuscript. We agree, however, that a differentiated discussion on how to apply case-only methods in the present context would provide useful information to readers. In our revised manuscript, at the end of the discussion
section, we carefully revised the following paragraph ... and added a differentiated discussion of case-only methods (with additional references).

“For the SOS studies, to estimate outcome risks with NSAID use in children and adolescents, we will consider case-only designs such as self-controlled case series or case-crossover.[26] One advantage is that case-only designs automatically control for all time-invariant confounders, measured or unmeasured (e.g., gender or genetics). They also produce better estimates in terms of statistical power to detect a safety signal when compared with cohort studies or case-control studies, thus offering a possibility to overcome limited data resources such as in the present context.[27] For several pediatric outcomes of interest, the occurrence of the event may change the probability of subsequent NSAID exposure, either by contraindication (e.g., acute renal failure and anaphylactic shock) or increased mortality risk (e.g., acute myocardial infarction and stroke), thereby violating the event-independent exposure assumption of the standard self-controlled case series method.[28] These issues can be addressed with case-only designs by use of either an advanced version of the self-controlled case series method[29-31] or a case-crossover design.[32] The case-crossover design considers only pre-event time and can be extended by methods such as the case-time-control design to account for time trends of drug exposure.[33, 34]”


The revised manuscript provides a differentiated discussion on case-only study designs in the context of pediatric drug safety research. As pointed out by the reviewer, the provision of useful guidance for readers on study design may increase the impact of the article. Therefore, we made the following additional modifications.

First, we added four words to the title (“... and which study designs ...”). The title now reads “Population-based analysis of non-steroidal anti-inflammatory drug use among children in four European countries. What size of data platforms and which study designs do we need to assess safety issues? The SOS project”.

Second, we added eleven words to the last sentence of the conclusion section of the abstract (... and the use of advanced versions of case-only study designs ...). The last sentence of the conclusion section of the abstract now reads “Even larger data platforms and the use of advanced versions of case-only study designs may be needed to conclusively assess the safety of these drugs in children.”.

Third, we added the following sentence to the conclusion section of the discussion. “Advanced versions of case-only study designs may be indicated to gain statistical power to study NSAID safety in children.”
Fourth, to include key words for case-only designs that could not be included neither in title nor abstract, we modified the key words as follows: “pharmacoepidemiology; database; drug utilization; health resource utilization; drug safety; sample size; Asthma exacerbation; self-controlled case series design; case-crossover design”.

**Statistical Comments**

4. The authors employ a purely frequentist approach to drug safety, seeking to establish testing threshold to estimate power to detect an association of size X. They have appropriately used one sided tests of statistical significance (as there is no plausible biology behind NSAID class medications protecting against many of the side effects mentioned. However, I would encourage the authors to consider if there is a less stringent testing threshold that might make sense in this context. I would suppose that most of the interest in NSAIDs here would be in comparative safety (as it seems unlikely that paracetamol or opioids would be alternatives and the absolute risks are small). It would be interesting if the authors might propose a threshold where a safety signal might be tentatively proposed, given the vulnerability of the underlying population.

Answer: We thank the reviewer for his positive comments about our statistical analysis. We agree that a less stringent testing threshold may be indicated in the context of NSAID safety signals in the pediatric population. We performed a sensitivity analysis for the power calculations using a less stringent alpha of 0.1 for an expected RR of 6, a ‘strong association’. This sensitivity analysis did not materially change our results. In our revised manuscript, we added the result of this calculation to Table 3. Furthermore, under “Limitations” in the discussion section, page 19, we added the following text.

“Some limitations should be considered. First, in this analysis, we primarily used alpha=0.05 as a testing threshold. To propose a tentative signal for NSAID safety in the pediatric population, a less stringent testing threshold may be indicated. For an expected RR of 6, a ‘strong association’, we performed additional power calculations with a less stringent alpha value of 0.1 (Table 3). This sensitivity analysis did not materially change our results.”

**Overall**

Excellent paper and it was an enjoyable read. It is a very hard problem, here, and I look forward to seeing continued work from the SOS project.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests: I declare that I have no competing interests

Answer: We thank the reviewer for his positive comments.
Referee 2, Roman Hudec:

1. The question is well defined

2. The methods are appropriate, widely and well described

3. Data are very interesting and good processed

4. The manuscript respect relevant standards for reporting

5. The discussion and conclusions are well balanced

Answer: Referring to points 1 to 5, we thank the reviewer for his positive comments.

6. Limitations of the work may be more clearly stated

Answer: We thank the reviewer for his time in carefully assessing the clarity of our manuscript. In our revised manuscript, at the end of the discussion section, starting on page 19, we carefully revised the following text to ensure clarity.

“Some limitations should be considered. First, in this analysis, we primarily used alpha=0.05 as a testing threshold. To propose a tentative signal for NSAID safety in the pediatric population, a less stringent testing threshold may be indicated. For an expected RR of 6, a ‘strong association’, we performed additional power calculations with a less stringent alpha value of 0.1 (Table 3). This sensitivity analysis did not materially change our results. Second, our study may not have captured all NSAID exposure, since many of these drugs are also available without prescription in all four countries. We expect any underestimation of NSAID use in the present study to be minor since most parents may be reluctant to administer drugs to their children without having consulted a health care professional. In addition, people are likely to prefer prescribed over freely available NSAIDs for financial reasons since reimbursement is only possible for prescribed drugs. Third, we observed that rates of NSAID use were low in the month of August. This is to be expected because of summer holiday periods during which physician or pharmacy visits are less likely to occur. Fourth, we only used diagnosis codes for identification of pediatric events of interest. We did neither use laboratory values, medical images nor procedures for event measurement, therefore potentially missing some events. We expect the amount of misclassification to be very minor since most patients with a confirmed diagnosis from these examinations would have a diagnosis code entered in the participating databases, as this is important for reimbursement. Fifth, we only considered the total person time of NSAID exposure, thereby possibly overestimating the possibilities of safety assessment. Issues such as gap lengths between subsequent NSAID prescriptions and switching between different substances would have to be accounted for by design of NSAID safety studies. Biases related to prevalent NSAID users can be avoided with a new-user study design.[25] With a new-user design, however, prevalent NSAID users would be excluded from the study cohort, thereby resulting in less exposure time than presented in this analysis.”

We also carefully revised and modified the subsequent paragraph of the discussion section. Please see our answer to the other reviewer’s point 3.
7. Acknowledgements are well described
8. The title is appropriate and abstract accurately convey what has been found
9. Acceptable

Answer: Referring to points 7 to 8, we thank the reviewer for his positive comments.

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 have no competing interests

Answer: We thank the reviewer for his positive comments.