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Reply to: Cause or consequence?

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Abstract:	

Title:

Reply to: Cause or consequence?

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Summary

SABINA III shows associations between SABA prescriptions and poor asthma outcomes and does not imply causation. However, implying that high SABA use is simply a "consequence" of poor asthma control is also an oversimplification of a complex issue.

Article

We thank Dr Volpe for questioning whether the results of the SABINA III study showing associations between SABA prescriptions and poor asthma outcomes should be regarded as "*cause or consequence*"[1]. We agree that causation cannot be assumed and stated this clearly as follows "*this cross-sectional study does not permit an assessment of a causal link between SABA prescriptions and asthma outcomes and does not discount reverse causality; the results simply represent an association*." [2] But implying that high levels of SABA use is simply a "*consequence*" is also an oversimplification of a complex issue. Firstly, besides the consistent results from epidemiologic studies there are many mechanistic studies of the negative effects of regular SABA use on biomarkers of airway inflammation, airway hyper-responsiveness, asthma symptom control and exacerbation risk, so causation is not ruled out [3,4]. Further, while logical to consider that high use of an as-needed medication for symptoms must represent poor control, we would point out that a central purpose of our paper was to assess not inhaler use, but SABA prescriptions by clinicians and purchase over the counter. These are systemic issues concerning physician behaviour and access to SABAs that, in the face of excessive use and poor asthma control, permit or even encourage SABA use, which is contrary to asthma guideline recommendations [5]. The "*long list*" of recommendations for addressing this situation is therefore highly pertinent to the objectives of the paper and we agree that these may, and in fact are intended to have "*profound implications …. for clinical practice and public health*" [5, 6, 7].

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Conflicts of interest

EDB is a member of the Science Committee and Board of GINA and reports personal fees from ALK, AstraZeneca, Boehringer Ingelheim, Chiesi, Menarini, Novartis, Orion, Regeneron Pharmaceuticals and Sanofi Genzyme. DBP has board membership with Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, Circassia, Mylan, Mundipharma, Novartis, Regeneron, Sanofi Genzyme, Teva Pharmaceuticals and Thermofisher; consultancy agreements with Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline (GSK), Mylan, Mundipharma, Novartis, Pfizer, Teva and Theravance; grants and unrestricted funding for investigator-initiated studies (conducted through Observational and Pragmatic Research Institute Pte Ltd) from AstraZeneca, Boehringer Ingelheim, Chiesi, Circassia, Mylan, Mundipharma, Novartis, Pfizer, Regeneron, Respiratory Effectiveness Group, Sanofi Genzyme, Teva, Theravance and UK National Health Service; payment for lectures/speaking engagements from AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, GSK, Kyorin, Mylan, Mundipharma, Novartis, Regeneron, Sanofi Genzyme and Teva; payment for the development of educational materials from Mundipharma and Novartis; payment for travel/accommodation/meeting expenses from AstraZeneca, Boehringer Ingelheim, Mundipharma, Mylan, Novartis and Thermofisher; funding for patient enrolment or completion of research from Novartis; stock/stock options from AKL Research and Development Ltd, which produces phytopharmaceuticals; owns 74% of the social enterprise Optimum Patient Care Ltd (Australia and UK) and 74% of Observational and Pragmatic Research Institute Pte Ltd (Singapore); is a peer reviewer for grant committees of the Efficacy and Mechanism Evaluation programme and Health Technology Assessment; and

was an expert witness for GSK. H-CW reports no disclosures. PS reports lectures on medical education and inclusion as a researcher on clinical study protocols funded by AstraZeneca, GSK, Teva, ITF Labomed, Boehringer Ingelheim and Sanofi Genzyme. AC and RJPvdV are employees of AstraZeneca. RJPvdV has shares in GSK and shares and options in AstraZeneca. MJHIB was an employee of AstraZeneca at the time the study was conducted and has shares in AstraZeneca.

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January 14, 2022

Prof. Paul O'Byrne
Section Editor
European Respiratory Journal

Dear Professor O'Byrne,

On behalf of my co-authors, I thank you for providing us the opportunity to respond to an article by Dr. Volpe (Ref: ERJ-03107-2021; Cause or Consequence?) critiquing our recently accepted manuscript, "Short-acting β_2-agonist prescriptions are associated with poor clinical outcomes of asthma: the multi-country, cross-sectional SABINA III study" (Ref: ERJ-01402-2021).

In our letter of response, we point out that Dr Volpe misread our report, in which we explicitly stated that the findings do not necessarily imply causality, but, as its aim clearly states, describes the prescribing of, and access to SABAs, which reflects physician behaviour and other systemic issues relating to SABA use and that this high level of access is contrary to the recommendations of asthma guidelines. Our paper suggests that this situation should be addressed and offers some options. The issue of causality was not addressed in our paper, although it may have played a role.

Thank you for considering our letter or response for publication.

Sincerely,

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