LETTERS

Weight Loss in Individuals with Obesity and Asthma

To the Editor:

We commend Okoniewski and colleagues for their recent systematic review published in AnnalsATS (1) on weight loss interventions in obese subjects with asthma, which we read with great interest. Although not cited by the authors, we note a comparable 2012 Cochrane review by Adeniyi and Young (2), which similarly assessed randomized controlled trials of weight loss interventions in asthma.

We draw your attention to the omission in the present review of at least one study eligible for inclusion (3) according to the a priori inclusion criteria, which did not restrict studies according to language of publication providing sufficient information in English was available for accurate data collection. This study had been published in Spanish but had been included in the aforementioned Cochrane review, for which the data were extracted and published in English. It is notable that the current review, as published, thus departs from its own protocol, registered in the International Prospective Register of Systematic Reviews (PROSPERO CRD42018085045).

We note also the inclusion of a study (4) of a population that combined subjects deemed to be "at high risk of asthma" with subjects with a diagnosis of asthma, despite no disaggregated data being published for these two groups.

Of 10 studies included in the review by Okoniewski and colleagues (1), only that by Stenius-Aarniala and colleagues (5) was published in full at the time of the Cochrane review, and it is striking that both reviews diverge in their assessment of the risk of bias in that study. The study by Stenius-Aarniala and colleagues is assessed in the current review as having low risk of bias in random sequence allocation but was deemed in the Cochrane review to be at unclear risk of bias, as the method used involved shuffling of cards yet produced equal numbers of participants in both groups, despite a small sample size. Conversely, the authors of the present review deemed the risk of attrition bias and reporting bias in this study to be unclear, whereas the authors of the Cochrane review found the Stenius-Aarniala and colleagues study to be at low risk of bias in these domains.

The current review also overlooks biased estimates in its qualitative analysis when referring to one study (6), which reported a significant improvement in FVC in liters ($P = 0.006$ between groups), but not FVC % predicted. It must be noted that the pertinent study used a per-protocol analysis, which did not include those patients randomized to intervention who achieved less than 10% weight loss. The published intent-to-treat analysis included only forced vital capacity (FVC) % predicted, and in this there was no significant between-group difference.

Finally, we must question the decision, in the protocol for the present review, to prioritize "relevant biomarkers (such as leptin, adiponectin, or IL-6)" as a primary outcome, with patient-important outcomes, such as asthma exacerbations, relegated to among the secondary outcomes or not listed at all (e.g., quality of life). These biomarkers were not included as either core or supplemental outcomes by an expert subcommittee convened by the National Institutes of Health and the Agency for Healthcare Research and Quality to propose which biomarkers should be assessed as standardized asthma outcomes in future clinical research studies—neither were they considered to be "emerging" (i.e., requiring validation and standardization) (7).

Notwithstanding these considerations, the review succeeds in highlighting the need for further well-designed randomized controlled trials investigating the effect of weight loss in obese asthma. As more recently approved obesity drugs, including liraglutide and lorcaserin, remain unstudied in this context to date, the time is ripe for such trials.

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References


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We appreciate the opportunity to address Dr. Watchorn and colleagues’ comments on our recent review on weight loss in obesity and asthma (1), which we wrote with the goal of summarizing current evidence, highlighting lessons from existing studies, and offering recommendations for future ones. We need effective lifestyle interventions for children and adults with obese asthma, and we are pleased that our review is drawing attention to the topic and stimulating discussion to advance this area of research.

There has been significant progress in recognizing the importance of risk-of-bias assessment, but it remains variable at best (2, 3), and it constitutes one of the challenges of producing high-quality systematic reviews (4). We judged the random sequence generation in the study by Stenius-Aarniala and colleagues (5) to present low risk, because it describes a random procedure performed by someone not involved in the study. Most reviewed studies were small, and we do not believe that achieving a balanced randomization should in and of itself raise suspicion. We considered the risk from selective outcome reporting to be unclear, because we did not find a registered protocol and could not evaluate whether all outcomes had been reported as stipulated a priori. We judged the overall risk of bias in this study to be moderate, and we stand by our appraisal.

Contrary to what Watchorn and colleagues state, the review protocol stated that the initial search would not have language restrictions but that studies should have enough information in English for accurate data collection. The abstract for Hernández Romero and colleagues (6) did not provide sufficient information on either intervention or outcomes, and thus it did not meet criteria for inclusion. However, for this response we reviewed the original manuscript in Spanish. The study compared two diets and reported improvements in obesity parameters and cytokines with both; in addition, it reported improvements in asthma symptoms and medication use with the diet based on jicama, cucumber, and a powder made of rice, soy, sesame seeds, and tuna fruit. Although the trial did not meet inclusion criteria, the results are consistent with other studies in the field. The study by Willeboordse and colleagues (7) indeed included children at “high risk” for asthma, as we clearly mention in the review. Moreover, the authors disclosed that ~66% of participants in their control group sought professional weight loss help. Both of these facts may have contributed to the lack of significant differences observed for some outcomes in that study.

We fully agree with Watchorn and colleagues that asthma symptoms and quality of life are important, and surely they noticed those outcomes are reported in the review. The distinction between “primary” and “secondary” outcomes was made a priori during protocol design, before performing the literature review, and it should be interpreted accordingly. In the actual publication, results are presented without attempts to prioritize certain outcomes or relegate others. The cited report on asthma biomarkers (8) is important, but it was certainly not aimed at the study of obesity and asthma. Our understanding of how obesity affects asthma is far from complete (9, 10), and examining relevant biomarkers in the setting of experimental weight loss and resultant asthma improvement will be crucial to understanding the underlying mechanisms. It is thus unsurprising that the majority of studies reviewed (as well as Hernández Romero and colleagues [6]) measured some type of biomarker. Given the heterogeneity of asthma, identifying novel biomarkers will be critical to help distinguish among asthma phenotypes and endotypes—including those related to obesity—and to identify new therapeutic targets for a more personalized treatment approach.

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