Letters to the Editor

Randomized controlled trial on weight loss in obstructive sleep apnea: inappropriate analysis limits main conclusion

Dear Sir:

The randomized controlled trial by Tuomilehto et al (1) in a recent issue of the Journal has provided much-needed insight into the long-term effects of a weight-loss program on mild obstructive sleep apnea in overweight and obese adults. Nevertheless, we are concerned about the robustness of the main conclusion, that weight loss improves obstructive sleep apnea, mainly due to a flawed intention-to-treat analysis. Two suggestions for how the authors may improve their analysis are provided here.

In randomized trials it is customary to perform an intention-to-treat analysis, in which subjects are analyzed according to their original allocation, irrespective of treatment actually received. This includes withdrawals, losses to follow-up, and crossovers. Data analysis that only includes data from completers is likely to have attrition bias (2–4). Known effects of attrition bias include overestimated treatment effects, reduced $P$ values, and increased between-trial heterogeneity (4).

Tuomilehto et al (1) claim to have performed an intention-to-treat analysis, but they appear to have analyzed data from the 71 completers only (out of 81 who were randomly assigned). This misinterpretation of the intention-to-treat principle is common (2, 3). Because the $P$ value for the main between-group analysis was high ($P = 0.049$), we wonder if the null hypothesis can still be rejected after a more appropriate handling of missing data to reduce attrition bias. This can, for example, be clarified by performing a sensitivity analysis in which baseline data are imputed at follow-up for patients who dropped out or by using multiple imputation for missing values (4).

Furthermore, by comparing change between groups from baseline to follow-up as the main analysis of treatment effect (see their Abstract and Table 3), there is no control for potential baseline imbalance because of regression to the mean (5, 6). Furthermore, one risks efficiency losses compared with an analysis of covariance (5). By using analysis of covariance of the apnea-hypopnea index at follow-up, not change from baseline to follow-up, with adjustment for baseline values, one can minimize confounding from regression to the mean and probably increase statistical power (5).

Readers may appreciate this study even more if the authors provide a conclusion based on these 2 suggestions.

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REFERENCES


Reply to E Hemmingsson et al

Dear Sir:

We appreciate the comments by Hemmingsson et al on our recent article (1). They raise important questions about statistical analyses of randomized controlled trials, and they further provide a critique on 2 aspects of our article: failure to account for possible regression-to-mean effect and improper use of the term intention-to-treat in our analysis. We are grateful for the possibility to respond to their comments, as their claims on inappropriate analyses are based on misunderstandings.

First, Hemmingsson et al correctly point out that, for analysis of treatment effect, the potential baseline imbalance should be accounted for to handle regression-to-mean effect, and this should preferably be conducted with analysis of covariance (ANCOVA) with adjustment for baseline values. We agree with this, and in fact

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this is exactly what we have done in our analyses. In our article, we state this in the “Statistical methods” section, as well as in the footnote of Table 3, and it is this baseline-adjusted result that is also given in the Abstract. Therefore, we find it difficult to understand how Hemmingsson et al could misinterpret this part of our analyses. One possible reason for their confusion is that we have used the change from baseline to follow-up as a dependent variable in the ANCOVA and, at the same time, adjusted for the baseline value. It might not be quite obvious, but it is well known (2) and easy to show (3) that this is fully equivalent to the proposed ANCOVA analysis “follow-up value adjusting for baseline value” when considering the estimation of the treatment effect.

Second, it is correct, as clearly stated in our article, that we performed the analyses only including those individuals who had complete follow-up data (and we did maintain the original, randomly assigned treatment of these individuals in all of the analyses). This approach leads to an unbiased estimate of the treatment effect under the assumption that missing data are “missing completely at random” (4). Hemmingsson et al claim that a more appropriate way to handle the missing data would be to impute the baseline values as follow-up values for those who did not complete the follow-up. However, whereas this kind of an analysis might under certain assumptions be more reasonable than the complete case analysis, there are no guarantees for that. Because this approach is one variant of last observation carried forward, it will produce biased estimates unless the underlying assumptions are fulfilled (5, 6).

We do agree with Hemmingsson et al that we should have presented a sensitivity analysis to our complete case analysis. Therefore, in our study, the difference in change in apnea-hypopnea index (AHI) was −3.3 (95% CI: −6.6, −0.1; \( P = 0.045 \)) when baseline values for those without follow-up data were imputed as follow-up values and with adjustment for the baseline value of AHI in the ANCOVA model. Furthermore, the odds ratio for having obstructive sleep apnea (OSA) at follow-up was 0.36 (95% CI: 0.14, 0.95; \( P = 0.038 \)) comparing the intervention group with the control group with this same approach and with adjustment for baseline AHI value.

Finally, and more generally, the use of the term intention-to-treat is complicated due to the fact that it actually implies complete follow-up of everyone in a study. If there are any missing data, as often is the case, then many different possibilities to handle the issue are available as shown above (eg, complete case analysis, imputing last observed values, multiple imputation, etc). Furthermore, because there are 2 different issues to be covered, the original random assignment to treatment and handling of the missing values, we believe that these cannot be covered by one simple statement such as “intention-to-treat,” without causing unnecessary confusion. This is now also recognized in the new version of the CONSORT (Consolidated Standards of Reporting Trials) statement guidelines for reporting parallel group randomized trials (7, 8), in which a more explicit statement on number of participants included in the analyses and information about retaining participants in their originally assigned groups are now requested, in contrast to the previously used “number of participants included in the analysis, and whether analysis was by intention-to-treat” (9). We fully support this new requirement, and we believe our way of reporting and stating the analysis population as we did (ie, “intention-to-treat principle in those who completed the follow-up,” together with a flow chart on study participants) is in line what is currently recommended by the CONSORT statement.

In conclusion, we have to keep in mind that statistics are only tools to interpret scientific information. Important ones, but not to be raised above the main message. Although the importance of weight loss in treating OSA has been recognized for >20 y, it has been commonly claimed that weight loss may not be enough when treating patients with OSA. Only during the last year have controlled intervention trials been published suggesting that these previous attitudes and suspicions should finally be reconsidered. In fact, weight loss with lifestyle intervention can be one of the rare curative treatments of OSA. We do hope that our reply clarifies the statistical remarks presented in the Hemmingsson et al’s letter and that the further discussion on the topic is focused on issues that really matter.

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REFERENCES