Response to Reviewers and Editor

Preoperative atelectasis in patients with obesity undergoing bariatric surgery: a cross-sectional study

Dear editor and reviewers,  
  
Thank you for taking the time to review our manuscript, for your interest in our study, and for your suggestions and comments, which we very much value. We have made significant efforts to discuss these thoroughly, respond to them, and incorporate any resulting modifications to our manuscript. You will find detailed and elaborate responses to your comments below.

## Section Editor

*Although the topic is of interest to the readers of this journal, the reviewers have raised some important concerns over the methodology of the study, including the number of confounders, imbalance between sex, etc. The authors should also better articulate the relevance of their findings in clinical practice.*

Thank you for recognizing that this is a topic of interest for readers of *Anesthesia & Analgesia*. Regarding the concerns over methodology and imbalance between sex, among others, we have responded to these individually in the subsequent responses to reviewers. We have also better articulated the relevance of our findings in clinical practice throughout the manuscript.

Regarding the overall concern of the selected confounders, as well as the definition of the exposures and outcomes, we would like to start our response by addressing this as we recognize that this was an important limitation of the prior version of our manuscript, which gave us the opportunity to review and re-frame the relationships of the variables in our study. After doing this and in response to the reviewers’ suggestions, we collected new relevant variables from the medical records by reviewing self-reported questionnaires that patients fill in at admission prior to surgery. The new variables collected included COPD, asthma, tuberculosis, use of supplementary oxygen at home, and use of CPAP at home. Likewise, we complemented obstructive sleep apnea status through self-reported history of OSA in addition to that consigned by the physician in the preanesthetic assessment.

In the following section, we describe the specific measures we took in order to strengthen the framework of the hypothesized relationships between variables in our study, ending with a description of the changes in the modelling strategy for the mediation analysis (inverse probability weighting), which constitutes a significant improvement that we consider adds robustness to our findings, while also improving our ability to communicate the clinical relevance of our findings to readers.

This re-framing involved the adoption of inverse probability weighting for the mediation analyses, in order to show that approximately 80% of the effect of BMI on SpO2 is mediated by atelectasis. We have now emphasized the clinical relevance of this finding as it is commonly thought that atelectasis found in chest CT in patients with obesity are caused by patient positioning in the supine position, due to excessive fat weight causing transient atelectasis, which are thought to disappear in the standing or seated position. Our study shows that atelectasis in the supine position also explain SpO2 levels measured in a different position (seated, at rest), reflecting that such atelectasis are not incidental findings. Lastly, we have significantly re-worked our manuscript’s structure in order to emphasize the potential implications of these findings for the perioperative management and mechanical ventilation of obese patients.

Lastly, we would like to emphasize that, besides being novel by describing a previously understudied phenomenon (atelectasis before surgery in obese patients), our study incorporated cutting-edge methods and statistical analyses, such as:

1. Incorporation of directed acyclic graphs to identify variables to adjust for in the models ([Lederer DJ, 2018](https://doi.org/10.1513/AnnalsATS.201808-564PS));
2. Modelling strategies for non-linear relationships with generalized additive models (i.e., [Enevoldsen J, 2024](https://doi.org/10.1007/s10877-023-01090-6));
3. Assessment of an ordinal mediator variable through inverse probability weighting, which allowed us to model a very challenging situation with shared exposure-outcome and mediator-outcome confounding with a method well-described in econometrics ([Huber M, 2014](https://doi.org/10.1002/jae.2341)) that is increasingly being applied in medicine;
4. Obtaining inverse probability weights through a machine learning-based method (non-parametric covariate balancing propensity scores) to allow for distribution-free modelling of the exposure and mediator when obtaining weights, thereby avoiding the risk of model misspecification, while also allowing us to obtain weights for a continuous exposure variable ([Fong C, 2018](https://doi.org/10.1214/17-AOAS1101)), something that is usually managed in a different way by researchers by creating binary categories in order to obtain weights for the commonly known situation of binary treatment exposures, which unfortunately leads to huge loss of information in the continuous variable; and
5. Open science. We advocate for full reproducibility and transparency in our study, reason why all our data and statistical analysis code are openly available through the websites cited in the manuscript. We hope that this will encourage other researchers to re-use our code while also allowing others to challenge our assumptions and reassess our study objectives with potentially different considerations to test the robustness of our findings and, hopefully, stimulate discussion of this topic among anesthesiologists and researchers in the field.

## Relationships between variables framework

### Systematic search of studies

We conducted a systematic search of studies to select the appropriate relationships between variables, according to the current evidence. This allowed us to review our directed acyclic graph (DAG), which we would like to emphasize, is the currently recommended method ([Lederer DJ, 2018](https://doi.org/10.1513/AnnalsATS.201808-564PS)) to select which *confounders* to adjust for, while identifying potential *mediators* (which **should not be adjusted for** in the models as this would incorrectly sweep away the effect of the main exposure variable of interest) and *colliders*, which should also not be adjusted for in the models as this could severely distort the relationships between exposure and outcome ([Griffith GJ, 2020](https://www.nature.com/articles/s41467-020-19478-2)).

The findings of the evidence of our search, described according to the nature of all relevant variables in our study, are summarized in the following DAG. We will subsequently explain what the individual arrows in this DAG mean, alongside their available evidence:

|  |
| --- |
| Directed Acyclic Graph, available in the manuscript as Supplementary Figure 1 |

The following information is also provided in the supplementary methods document.

### Exposure

The increasing degree of obesity, according to the WHO obesity class categories or BMI, is the exposure of interest and is represented with a green node (type\_obesity).

### Primary outcome

Having atelectasis (Yes or No) in the prevalence ratio models, and an increasing degree of atelectasis (atelectasis percent) in the ordinal regression models are the main outcomes of interest. A green arrow from type\_obesity to atelectasis\_percent represents the exposure-outcome relationship of interest in the DAG.

### Secondary outcome

Decreasing preoperative SpO2 is hypothesized to be related to an increasing degree of obesity. An arrow from type\_obesity to spo2\_VPO at the upper part of the figure represents this. Atelectasis\_percentage is thought to be the main mediator of the effect of BMI on preoperative SpO2. An arrow from type\_obesity to atelectasis\_percent, followed by an arrow from atelectasis\_percent to spo2\_VPO.

### Covariates

#### Sex and Age

These two variables are known to be associated with a higher risk of developing postoperative atelectasis in patients with obesity undergoing bariatric surgery ([Baltieri L, 2016](https://doi.org/10.1016/j.bjane.2014.11.016)). Arrows originating from these variables and going to type\_obesity, atelectasis\_percent, and spo2\_VPO represent these relationships.  
The implications for statistical analyses is that ***sex*** and ***age*** are both **confounders** to be accounted for in both of the models with atelectasis and SpO2 as outcomes.

#### Obstructive sleep apnea

Increasing BMI is a strong risk factor for OSA and OSA severity ([Baltieri L, 2016](https://doi.org/10.1016/j.bjane.2014.11.016)). In a directed acyclic graph, all arrows should have a single direction. Since obesity is the risk factor leading to development of obstructive sleep apnea, and not the other way around ([Romero-Corral A, 2010](https://doi.org/10.1378/chest.09-0360)), an arrow originating in type\_obesity, pointing towards OSA represents this relationship. Thus, OSA is hypothesized to lead to the degree of atelectasis and preoperative SpO2. Therefore, an arrow from OSA to atelectasis\_percent and spo2\_VPO represents these relationships. The implications for the analysis are the following:

1. OSA is a potential **mediator** of the effect of BMI on atelectasis percentage. Therefore, this variable should **not** be adjusted for in the models with ***atelectasis*** as the outcome.
2. OSA is a **confounder** of the mediator-outcome relationship in the models with ***SpO2*** as the outcome.

#### Asthma

It has been shown that obesity leads to asthma, whereas the inverse relationship is very unlikely to be possible ([Chen YC, 2018](https://www.nature.com/articles/s41366-018-0160-8)). Thus, an arrow from type obesity to asthma was drawn.

It has been reported that obesity-associated late onset non-allergic asthma is negatively related to atelectasis due to a tendency to develop more air trapping than atelectasis in these patients, compared to patients with obesity and no diagnosis of asthma in whom the airways collapse slowly and air is expelled, leading to atelectasis ([Bhatawadekar SA, 2022](https://www.atsjournals.org/doi/10.1513/AnnalsATS.202010-1317RL)). During sleep, asthma affects SpO2 independently of BMI and OSA ([Sundbom F, 2022](https://doi.org/10.5664/jcsm.10178)). For these reasons, an arrow from asthma to atelectasis, and an arrow from asthma to SpO2 was drawn.

The implications for the analysis are the following:

1. Asthma is a potential **mediator** of the effect of BMI on atelectasis percentage. Therefore, this variable should **not** be adjusted for in the models with ***atelectasis*** as the outcome.
2. Asthma is a potential **confounder** of the mediator-outcome relationship in the models with ***SpO2*** as the outcome.

#### COPD

Although there is a strong relationship between undernutrition and COPD, the relationship between obesity and COPD has been inconsistent among studies. Since this study only included patients with obesity, the potential relationship between underweight and COPD is likely not relevant for this particular study. Furthermore, there is still doubt regarding any potential role of obesity-related pathophysiological mechanisms which could potentially lead to COPD ([Hanson C, 2014](https://doi.org/10.2147/copd.s50111)). For these reasons, an arrow between COPD and obesity was not drawn. This assumption was checked through the conditional independencies checking method (see Part 4 report on github), thus confirming that this assumption is consistent with the data.

Regarding a relationship between COPD and SpO2, there is a clear relationship between these variables, reason why an arrow going from COPD to SpO2 was drawn. As for atelectasis, studies have found atelectasis is related with COPD, especially in patients with wood smoke-related COPD ([González-García M, 2013](https://doi.org/10.1590/s1806-37132013000200005)) and ([Carmo Moreira MA, 2013](https://doi.org/10.1590/s1806-37132013000200006)). Thus, an arrow from COPD to atelectasis was drawn.

The implications for the analysis are the following:

1. COPD is **not** a potential confounder of the effect of BMI on atelectasis percentage. Therefore, this variable should **not** be adjusted for in the models with ***atelectasis*** as the outcome.
2. COPD is a potential **confounder** of the mediator-outcome relationship in the models with ***SpO2*** as the outcome.

#### Altitude

Although not directly linked to obesity, participants with OSA at an an altitude above 1600 meters can develop hypobaric hypoxia, which “promotes frequent central apneas in addition to obstructive events, resulting in combined intermittent and sustained hypoxia” ([Bloch KE, 2015](https://doi.org/10.1089/ham.2015.0016)).

For the atelectasis outcome, we did not find evidence either supporting or rejecting an association between altitude and prevalence of atelectasis. However, during the conditional independencies assumptions testing procedure, the data suggested a correlation, reason why an arrow from altitude to atelectasis was drawn as the reverse is less likely to be true (i.e., obesity would hardly determine the altitude of the place of residence).

The implication for analysis is that ***altitude\_cat*** is a potential **confounder** to be accounted for in both models (with atelectasis and SpO2 as outcomes).

#### Oxygen use at home and CPAP use at home

These variables are **colliders** and **descendants** of the exposure, mediator, outcomes, and covariates of interest. The implications for analyses are that these 2 variables should **not** be adjusted for in any of the models as this would introduce **collider bias**.

#### Hemoglobin

There is no strong evidence supporting a link between BMI and hemoglobin. In any case, hemoglobin would be a descendant of all main variables of interest (exposure, mediator, and outcomes). Thus, hemoglobin was excluded from this DAG for simplification.

#### Other variables

Other variables that are potential confounders are not shown in this DAG since they were addressed by design in this study as follows:

* Current COVID-19: Exclusion criteria were applied to **n=2** patients with CO-RADS 3 and **n=2** with CO-RADS 4. Only participants with low probability of COVID-19 (CO-RADS 1 and 2) were included in this study.
* Prior COVID-19: This was an exclusion criterion (**n=3**).
* Bronchiectasis in chest CT: This was an exclusion criterion (n=0).
* Neuromuscular diseases: This was an exclusion criterion (n=0).
* Prior or current history of tuberculosis: This was an exclusion criterion (n=0).

#### Unmeasured variables

Due to the possibility of unmeasured confounders, E-values were calculated and presented when possible as sensitivity analyses.

## Reviewer 1

*Interesting retrospective/prospective cohort study utilizing imaging derived by CT scanning during COVID pretesting and evaluation of the prevalence of atelectasis in obesity. Overall, the topic is interesting and bring to the attention the far more common presence of atelectasis in obesity (graded by BMI class, therefore standardizing through stratification).*

Thank you for your positive appreciation of our study in this sense.

*The clinical relevance of the finding though is elusive, meaning atelectasis may be dynamic and also dependant on other factors that were present during that time and maybe resolvable.*

hh

*The other issue is that the study did not take into consideration OSA risks factors and known/predicted hx of OSA*.

hh

*The data also may be skewed due to 90% of female subjects*.

hh

*Regarding the manuscript need a significant refocusing. There are too many distractors and needs a simplification of subjects covered, as well as more patients info/demographic.*

hh

*. The all explanation of the testing story is way too long. I think the subject is academically interesting yet in the current presentation does not add much more than knowing atelectasis is very frequent in obese patients.*

hh

## Reviewer 2

*The objective of the study is to determine the prevalence of preoperative atelectasis in patients undergoing bariatric surgery and what impact does the extent of atelectasis have on preoperative SpO2 in the seated position? The authors found that preoperative atelectasis were highly prevalent in patients with obesity undergoing bariatric surgery 32.6% (95%CI: 27.0-38.9) and a BMI above 45 was associated with a higher relative prevalence and atelectasis percentage coverage, the latter explaining ~70% of variation in preoperative SpO2. The authors was able to do this due to COVID 19 and the opportunity to have data on preoperative chest computed tomographies. There are a number of points in the manuscript that need further clarification.*

hh

#### Introduction and methods

*The authors stated, “The important risk factor for lung complications (i.e., atelectasis) in patients undergoing anesthesia as these patients suffer from lung restriction”. What is meant by lung restriction?*

hh

*Lagier D, Zeng C, Fernandez-Bustamante A, Vidal Melo MF. Perioperative Pulmonary Atelectasis: Part II. Clinical Implications., 2022.”Lagier and cols. recently highlighted that the direct impact of intraoperative pulmonary atelectasis on postoperative outcomes is still unclear. Reference given was Lagier D, Zeng C, Fernandez-Bustamante A, Vidal Melo MF. Perioperative Pulmonary Atelectasis: Part II. Clinical Implications., 2022. Suggest to use Lagier et al… Also, is the a book chapter? Need publisher and editor and page number etc*

hh

*Exclusion criteria were a CO-RADS score ≥3, positive antibody test against SARS-CoV-2, and a prior history of COVID-19, neuromuscular disease, or bronchiectasis. Please clarify what CO-RADS score.*

hh

*The authors stated. “Obesity class categories were created from BMI according to WHO criteria:2 class 1 (3035), 2 (3540), and 3 (≥40). Throughout the manuscript, there is an absence of units for BMI. Need to be clearly written.*

hh

*“Thus, all patients with an atelectasis percentage ≥2.5% were classified as having atelectasis.” There is no reference on this statement. Since this study is entirely based on this classification for atelectasis. Please give supporting reference.*

hh

#### Results

*“Patients with a diagnosis of OSA constituted 7.6% (n=18) of the sample”. Please clarify how OSA was diagnosed.*

hh

*“When examining this by obesity class, laterality was not significantly different forthose with class 1, 2, and 3 obesity categories: n=7 (87.5%), n=10 (66.7%), and n=36 (66.7%) respectively (p=0.484).” What is meant by laterality?*

hh

*“The mean atelectasis percentage coverage in the sample was 2.66% (95%CI:2.08-3.26) and according to WHO categories: class 1 (0.93%, 95%CI:0.32-1.81), class 2 (1.55%, 95%CI:0.75-2.45), and class 3 (4.04%, 95%CI:3.06-5.02). Within class 3 subgroups, the mean atelectasis percentage was 0.7% (95%CI:0.22-1.27) in the 40-45 group; 3.63% (95%CI:2.18-5.0), in 45-50; and 10.44% (95%CI:8.83-12.5), in the ≥50 subgroup” Need unit for BMI.*

hh

*Age was similarly distributed among patients without atelectasis (40.6, SD:10.1) and those with atelectasis (39.6, SD:9.3) (p=0.498). Please put unit*

hh

*SpO2 was significantly lower in patients with atelectasis (92, IQR: 91-93) compared to those without (97, IQR: 96-98) (p<0.001), and lower in patients with bilateral atelectasis (91.5, IQR: 90-92) compared to those with unilateral atelectasis (92, IQR: 92-93) (p=0.006). Please put unit.*

hh

*“We found a mean overall atelectasis percentage (as a fraction of total lung volume) of 2.66% (95%CI:2.08-3.26), which is close to the 2.1% reported by Eichenberger, et al.8 Reinius and cols. reported lower numbers (0.4 ± 0.7%),15 although their measurement was at the end of espiration and their estimate could be biased to the null due to zero-inflation as suggested by the SD which includes negative values.” A typo “espiration”*

hh

*“We observed that only categories above 45 had a significantly higher odds of increased atelectasis percentage coverage con chest CT after adjusting for confounders”. What is “con chest CT”?*

hh

*We observed that BMI, OSA, and atelectasis percentage were all significantly associated with SpO2 in univariable models. Nonetheless, when adjusted for atelectasis percentage, only atelectasis percentage remained significantly associated with atelectasis percentage. Please clarify what is meant by “only atelectasis percentage remained significantly associated with atelectasis percentage”.*

hh

*Noteworthy, there was heteroskedasticity in the residuals of adjusted models, with very low error at SpO2 ≤95% and increasing error at higher SpO2 values, possibly reflecting that explanation of decreased SpO2 values by these variables was very good, but that SpO2 values >96% were not well explained by these terms. What do the authors meant by heteroskedasticity?*

hh

*In Table 1, the biochemistry information are not needed*

hh

*Table 3 . Univariable and multivariable ordinal logistic regression models of lung atelectasis percentage coverage. Please give the factors for multivariable ordinal logical regression models.*

hh

## Reviewer 3

*Thank you for the opportunity to review this manuscript. Please have the whole manuscript reviewed and revised to improve English grammar and usage.*

hh

*Thank you for the opportunity to review this manuscript. Please have the whole manuscript reviewed and revised to improve English grammar and usage. Overall the manuscript is well-written and well describes the key aspects of the performed study.*

hh

*In the Introduction, P6L18, please elaborate on the said, “exposure-response pattern” and quantify if possible.*

hh

*In the Introduction, P7L7, please state a study hypothesis. Please state and define the exposure and the outcome.*

hh

*In the Methods section, P8L17, please spell out the abbreviation “CO-RADS” on first use and explain the score. Please apply this comment to all other abbreviations.*

hh

*In the Discussion section, P20L7, the authors might consider adding a paragraph explaining their choice to limit the scope of their study to the pre-op period only and not trying to correlate pre-op atelectasis and oxygenation data with any available intra-op and post-op related outcomes.*

hh

*Overall, this is a well-written manuscript with specific and minor limitations as stated above.*

hh