Bukti Komunikasi dengan Jurnal

REBUTTAL FOR REVIEWER 1

Reviewer 1:

English Language and Style

( ) Extensive editing of English language and style required
( ) Moderate English changes required
(x) English language and style are fine/minor spell check required
( ) I don't feel qualified to judge about the English Language and Style

Response to Reviewer 1 (English Language and Style):
Dear Reviewer 1,

We thank the reviewer for this comment. The manuscript has been carefully revised for English language, grammar, and style. Minor edits were made to improve clarity and readability.

Dear Reviewer 1,

Thank you for your thorough review and insightful comments on our manuscript. We appreciate your detailed feedback, which has significantly helped to improve the quality of our work. We have carefully considered each of your points and and we appreciate the opportunity to clarify our approach and its rationale. **Revisions have been highlighted in yellow** throughout the manuscript for clarity.

Below is our point-by-point response to your comments.

Comment 1. The exposure assessment methodology is fundamentally flawed. Using area-level PM2.5 measurements from monitoring stations to assign individual exposure classifications creates significant misclassification bias. Children move between microenvironments (home, school, transport) with varying pollution levels. The authors must either:

1. Conduct personal exposure monitoring using portable PM2.5 monitors
2. Develop time-weighted exposure models incorporating indoor/outdoor ratios
3. Acknowledge this as a major limitation that prevents causal inference

The sample size calculation appears post-hoc. With only 107 participants, the multivariate model is likely overfitted (fewer than 10 events per variable). The study lacks power to detect interaction effects or properly adjust for multiple confounders simultaneously.

Response:

The reviewer correctly notes the limitations of using area-level PM2.5 measurements instead of individual or time-weighted exposure models. We acknowledge that the **mapping-based air**

quality survey provides an estimation of exposure and **may not fully capture individual exposure fluctuations**. However, we chose this method for its **practicality and feasibility** within the scope and resources of our study, which was a critical first step in identifying appropriate high- and low-exposure schools.

The gold standard methods, such as **personal exposure monitoring** and **time-weighted exposure models**, were indeed considered. However, their implementation was technically and logistically infeasible for the initial phase of our study, which required a rapid and cost-effective method to survey broad areas and identify schools with contrasting exposure levels. **Conducting personal exposure monitoring for each participant across a large, undefined geographical area would have been prohibitively expensive and logistically complex.** Similarly, **time-weighted models were not feasible as they require detailed activity data and microenvironment concentrations that were not available at this stage.**

Our **mapping-based survey** provided a **robust** and **defensible method** for achieving our study's primary objective: to identify two distinct study populations—one with high PM2.5 exposure and one with low exposure. The significant differences in PM2.5 concentrations between these two groups, as outlined in our results, confirm the effectiveness of this approach. While we acknowledge that this method does not capture the full complexity of individual exposure, we believe it provided a sufficient basis to test our hypothesis within the constraints of our cross-sectional design. We have further clarified this reasoning in **PM2.5 Measurement** section in **Methods**, and the study's limitations in the **"Study Limitations"** section of the revised manuscript.

Regarding the sample size calculation, we would like to clarify that the sample size was determined **a priori** (not post hoc) as described in detail in the **"Sample Size Determination"** section of the Methods. This calculation was based on detecting a significant difference in the prevalence of RTI between the two exposure groups. While the final number of participants (n=107) and events (50 RTI cases) meets the minimal 10:1 ratio for our final multivariate model, we agree that this limitation introduces **a risk of overfitting** and **reduces the statistical power** to detect smaller effects or interaction terms.

To address these concerns directly, we have taken several steps in the revised manuscript:

- We conducted a series of **sensitivity analyses** to evaluate the robustness of our key finding, the odds ratio for PM2.5. These analyses demonstrated that the association remains consistent across different model specifications, suggesting that our main finding is **robust** and not a result of overfitting.
- We have included the results of the **Hosmer-Lemeshow test** and a brief discussion of **residual plots** in the **Results** section. These diagnostic checks confirmed that our final multivariate model **exhibits a good fit to the data**, further mitigating concerns about model validity.

- In the **"Study Limitations"** section, we have added a dedicated paragraph acknowledging the potential for unmeasured confounding and the limited power to detect interaction effects. We explicitly state that while our findings are compelling, they should be interpreted with caution, especially given the sample size constraints.

These revisions demonstrate that while our study has limitations, **our statistical methods are sound**, and **our key findings are robust**.

Comment 2: The study conflates geographical differences with PM2.5 exposure effects. Jakarta and Bandung differ substantially in climate, altitude, socioeconomic composition, healthcare access, and other pollutants beyond PM2.5. The observed association could reflect any of these unmeasured factors rather than PM2.5 specifically.

The exposure contrast is poorly characterized - only showing PM2.5 levels at study sites without temporal variability, seasonal patterns, or co-pollutant profiles. Children in Jakarta likely experience different pollution mixtures (higher NO2, SO2, ultrafine particles) that could drive respiratory effects.

Response:

Thank you again for your very detailed and insightful comments. We have carefully considered your feedback regarding the potential for confounding factors and the characterization of our exposure data. Below is our point-by-point response to your second comment.

We agree that comparing two different cities may introduce potential confounding by geography, since Jakarta and Bandung differ in climate, altitude, socioeconomic composition, healthcare access, and other environmental characteristics. **We acknowledge that environmental conditions such as altitude, colder temperatures, and humidity have been associated with increased respiratory susceptibility and viral persistence. However, in our study, RTI prevalence was actually substantially higher in Jakarta (lower altitude, warmer climate) compared to Bandung (higher altitude, cooler climate). This suggests that geographical and climatic differences are unlikely to be the primary drivers of the observed association.**

To reduce bias further, we deliberately selected school communities with broadly similar socioeconomic backgrounds and applied strict inclusion and exclusion criteria (e.g., excluding children with malnutrition, smoking exposure, or chronic diseases). Baseline characteristics showed no significant differences in age, gender, maternal education, or maternal occupation between the two groups, suggesting reasonable comparability at the individual level. Nutritional status and immunization history were controlled by inclusion criteria (only children with normal nutrition and complete immunization were enrolled). RTI was assessed directly by interview and examination, so healthcare access did not affect case ascertainment. Although income and housing were not measured, all participants were from government elementary schools and maternal education/occupation were comparable across sites, suggesting minimal socioeconomic differences. Residual confounding, however, cannot be ompletely excluded and is acknowledged as a limitation.

We also acknowledge that our exposure assessment was limited to PM2.5 measurements taken at the study sites and did not capture temporal variability, seasonal changes, or co-pollutant concentrations such as NO_2, SO_2, or ultrafine particles. Therefore, our study cannot fully disentangle the specific effect of PM2.5 from other correlated pollutants or from broader contextual differences between Jakarta and Bandung. We have clarified this limitation in the revised manuscript.

We agree with the reviewer that other air pollutants (e.g., NO_2, SO_2, ozone, ultrafine particles) may also contribute to respiratory infections and could confound or modify the observed association. Unfortunately, only PM2.5 measurements were available for our study, and we therefore could not evaluate the role of co-pollutants. We have now acknowledged this as a limitation in the revised discussion. Nevertheless, PM2.5 is widely regarded as the most reliable proxy of overall air pollution burden and has been consistently associated with respiratory morbidity in children across numerous international studies. Given the substantially higher PM2.5 concentrations observed in Jakarta compared with Bandung, we believe that PM2.5 remains the most plausible explanation for the increased RTI prevalence observed in our study population.

Finally, we would note that if altitude or climatic conditions were the primary determinants of RTI risk, one would expect a higher prevalence in Bandung (higher altitude, cooler climate). In fact, RTI prevalence was substantially higher in Jakarta, supporting the interpretation that higher ambient pollution levels—particularly PM2.5, which was consistently elevated in Jakarta—likely played a more dominant role in driving the observed association. While our study cannot establish causality or pollutant-specific attribution, it provides valuable local evidence consistent with the broader global literature linking air pollution, and PM2.5 in particular, with increased respiratory morbidity in children.

Comment 3: The odds ratio of 7.167 is implausibly large for environmental exposure studies and suggests unmeasured confounding. The authors correctly note OR overestimation with common outcomes but don't adequately address this limitation.

The multivariate model includes only 4 covariates with 50 RTI events, meeting the 10:1 rule minimally, but several important confounders are omitted (household income, indoor air quality, previous RTI history). Model diagnostics (Hosmer-Lemeshow test, residual plots) are not reported.

Response:

We thank the reviewer for this insightful comment. We agree that the odds ratio of 7.167 is unusually large compared with most environmental epidemiology studies and may represent overestimation rather than a true causal effect. Overestimation is particularly likely in our study because RTI was relatively common, and odds ratios are known to exaggerate effect sizes when outcomes are prevalent. In addition, residual confounding from unmeasured variables (e.g., household income, indoor air quality, prior RTI history) may have further inflated the observed association.

Our multivariate logistic regression included PM2.5 exposure plus four covariates (age, gender, maternal education, maternal occupation), yielding ~50 events across 5 predictors, which meets the conventional 10 EPV rule. While this suggests that overfitting was not severe, we acknowledge that our small sample size limited the inclusion of additional covariates and increased the potential for unstable estimates. Thus, the large OR should be interpreted with caution as an exploratory finding rather than a precise risk estimate.

To address this concern, we have:

1. Expanded the discussion to explicitly distinguish between overestimation of effect size (due to common outcome and unmeasured confounding) and overfitting (due to small sample size and limited covariates).
2. Reported the Hosmer–Lemeshow test ($\chi^2 = 4.643$, df = 8, $p = 0.795$) and residual plots, which indicated good model fit and no influential outliers.
3. Conducted sensitivity analyses showing that the association between PM2.5 and RTI remained consistent across different model specifications, which increases confidence in the robustness of our main finding.

We have also added a clear statement in the revised "Study Limitations" that, while the association between PM2.5 and RTI is robust across different models, the magnitude of the effect is likely overestimated and should be interpreted with caution.

Comment 4. The policy conclusions are overstated given the methodological limitations. While the authors appropriately call for air quality improvements, the evidence base from this single cross-sectional study cannot support specific intervention recommendations.

The socioeconomic analysis is superficial. Maternal education categories (none to junior high vs. senior high) don't capture the nuanced relationship between SES and health outcomes. The finding of no SES-RTI association contradicts extensive literature and suggests measurement inadequacy rather than true absence of effect.

Response:

Thank you for these thoughtful comments. We agree that the policy conclusions in our initial draft may have been overstated given the inherent limitations of a single cross-sectional study. In the revised version, we have tempered our language to emphasize that our findings provide preliminary evidence supporting the importance of air quality improvement, but cannot establish causality or justify specific intervention recommendations. Instead, we highlight the need for further longitudinal and multipollutant studies to better inform policy.

Regarding socioeconomic status, we acknowledge that our analysis was limited to maternal education and occupation as proxy indicators of SES. While these variables are commonly used in child health research, they do not fully capture the complex and multidimensional nature of socioeconomic position, such as household income, housing quality, or paternal occupation. The absence of an observed association between maternal education and RTI in our study should therefore be interpreted cautiously and may reflect measurement limitations rather than a true lack of effect. We have clarified this in the discussion and noted the importance of including more comprehensive SES measures in future studies. **Nevertheless, despite these limitations, our study provides valuable local evidence from Indonesia consistent with the broader global literature linking air pollution—particularly PM2.5—to adverse respiratory outcomes in children.**

We sincerely thank Reviewer 1 for the thoughtful and comprehensive critique. The comments have been invaluable in strengthening our manuscript, prompting a thorough re-evaluation of our methodology, analysis, and interpretation of findings. We believe that the revised manuscript is significantly improved by the inclusion of more detailed explanations, a more robust statistical analysis, and a transparent acknowledgment of the study's limitations. We are confident that these revisions have enhanced the scientific rigor and credibility of our work, allowing for a more accurate and responsible presentation of our findings. We hope that these changes adequately address all the concerns raised and that the revised manuscript meets the high standards of this journal.

Sincerely,

Hari Krismanuel
Universitas Trisakti
hari_krismanuel@trisakti.ac.id

REBUTTAL FOR REVIEWER 2

English Language and Style

( ) Extensive editing of English language and style required
(x) Moderate English changes required
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Response to Reviewer 2 (English Language and Style):
Dear Reviewer 2,

We thank the reviewer for this comment. The manuscript has been carefully revised for English language, grammar, and style. Minor edits were made to improve clarity and readability.

Dear Reviewer 2,

Thank you for your valuable feedback, Reviewer 2. Your input is very helpful in refining our manuscript, particularly concerning the validity and interpretation of our findings. Here is our response to the points you raised. **Revisions have been highlighted in yellow** throughout the manuscript for clarity.

Comment 1: The cross-sectional design limits causal inference. While the statistical association is strong, temporality cannot be established. Stronger cautionary language should be used in the conclusions.

Response:
We fully agree with this observation. The reviewer is correct that the cross-sectional design of our study prevents us from establishing temporality and making a causal inference. As advised, we have revised the **Abstract** and **Conclusion** sections to use more cautious and precise language, replacing any terms that might imply causality with wording such as "**association**" and "**related**," to ensure consistency with the study design. In addition, we emphasize in the revised discussion that longitudinal studies will be needed in the future to establish temporal and causal links more definitively.

Comment 2: Logistic regression with a relatively small sample (n=107) and multiple covariates risks overfitting. The authors note this but should consider presenting sensitivity analyses - validation process of RAAEC-C is not fully described.

Response:

We thank the reviewer for this important observation. We acknowledge that logistic regression with a relatively small sample size and several covariates may increase the risk of overfitting. As noted in the manuscript, our model was based on approximately 10 events per variable, which is considered the minimal acceptable threshold in logistic regression. To further address this concern, we conducted **sensitivity analyses** by **fitting models with a reduced set of covariates**, as well as models including only PM2.5 exposure. These analyses yielded results **consistent in direction and magnitude with our main model**, suggesting that **the association is robust**. We have added a description of this sensitivity check in the revised Statistical Analysis, and Results sections.

In addition, we confirm that model diagnostics were performed. The **Hosmer–Lemeshow test** showed good model fit ($\chi^2 = 4.643$, df = 8, p = 0.795), the classification table indicated approximately 72.9% correct classification, and residual plots (standardized residuals vs predicted probability) showed no systematic pattern or influential outliers. These findings support the **adequacy and stability** of our multivariate model.

Regarding the RAAEC-C instrument, we have expanded the Methods section to describe its development and validation process more clearly. The RAAEC-C instrument was developed for this study, based on established global protocols for childhood illnesses and respiratory assessment [28,29,30,31].

To ensure its validity and reliability for this specific population, a rigorous validation process was conducted. Its content validity was confirmed through an expert review, with the Content Validity Index (CVI) indicating satisfactory relevance and comprehensiveness.

Furthermore, its reliability was confirmed by assessing inter-rater agreement. This analysis was performed on the categorical diagnosis using Cohen's Kappa to confirm a high level of consistency among assessors. Additionally, the consistency of continuous measurements, such as BMI-for-age z-scores, and anthropometric indicators, was confirmed with the Intraclass Correlation Coefficient (ICC). These details are now included in the revised manuscript.

Comment 3: There are some areas where the language could be improved for conciseness, style, and grammar.

Response:

We thank the reviewer for this helpful comment. The manuscript has been carefully revised to improve conciseness, style, and grammar. Several sentences have been restructured for clarity, redundant wording has been removed, and minor grammatical errors have been corrected. We believe these changes have improved the readability and flow of the manuscript.

Comment 4: A higher prevalence in one area compared to another might depend on a fortuitous higher circulation of a virus. How did the authors account for this?

Response:

We thank the reviewer for raising this important point. We acknowledge that differences in RTI prevalence could in part be influenced by temporal variation in viral circulation, and this potential bias cannot be completely excluded. To minimize seasonal effects, data collection in both sites was conducted during the same season. Importantly, if viral circulation alone were the dominant explanation, one might expect a higher RTI prevalence in Pangalengan, which has a cooler climate, higher altitude, and lower absolute humidity but often higher relative humidity—conditions known to favor viral persistence and impair mucosal defenses. In contrast, our study found substantially higher RTI prevalence in Jakarta. This pattern suggests that while temporal variation in respiratory virus circulation remains a limitation, the large difference in PM2.5 exposure between Jakarta and Bandung is a more plausible driver of the observed association. We have clarified this point in the revised discussion.

Comment 5: Relevant recent studies on air pollution and respiratory infections are missing and not discussed: e.g. PMID: 40358039, PMID: 36282132, PMID: 3847052, PMID: 29940478. Despite on lower tract infections, such a studies should be considered to corroborate the hypothesis and interpret the data.

Response:

We thank the reviewer for pointing out the need to incorporate additional recent studies. We have now revised the discussion to include this broader literature. Specifically, several new studies corroborate our findings: **Comotti et al. (2025)** reported that air pollution exposure significantly increased hospitalization risk in infants with bronchiolitis (PMID: 40358039). Similarly, **Milani et al. (2022)** demonstrated in a prospective cohort that short-term exposure to PM2.5 and PM10 was associated with greater bronchiolitis severity, particularly RSV-related cases (PMID: 36282132). In a more recent case–control study, **Van Brusselen et al. (2024)** found that both short- and medium-term exposure to particulate matter and NO_2 were linked to increased bronchiolitis risk in infants (PMID: 38470521). Finally, **Carugno et al. (2018)** conducted a systematic review and meta-analysis that confirmed consistent associations between PM2.5, PM10, and NO_2 exposure and increased bronchiolitis hospitalizations across multiple studies (PMID: 29940478).

Together, these studies strengthen the biological plausibility and external validity of our results, situating our findings within a growing body of evidence that air pollution—particularly PM2.5—plays a major role in the burden of pediatric respiratory infections.

We believe these revisions fully address your concerns and significantly improve the quality and rigor of our manuscript.

We sincerely thank Reviewer 2 for the insightful and constructive comments. Your feedback has been invaluable in strengthening our manuscript, prompting us to clarify our methodology, refine our language, and more transparently address the study's limitations. We are confident that these revisions have significantly improved the scientific rigor and overall quality of our work. We believe our revised manuscript now more accurately and robustly presents our findings, and we hope it meets the high standards of this journal.

Sincerely,

Hari Krismanuel
Universitas Trisakti
hari_krismanuel@trisakti.ac.id

Screenshot manuscript dipublikasi di jurnal Scopus 1 di akun SINTA