Peer Review File

Article information: https://dx.doi.org/10.21037/jtd-2025-319

Review Comments

Comment 1: *I have some concerns for this study. First, the analysis relied on prebronchodilator spirometry data, as postbronchodilator measurements were only available for a subset of participants; previous research suggests postbronchodilator data may better predict mortality, which could affect result accuracy.*

Reply: Thank you for your detailed review and constructive comments on our study. We appreciate your concerns regarding the reliance on pre-bronchodilator spirometry data. Because the NHANES conducted the postbronchodilator spirometry in only a subset of patients with obstructive pulmonary disease, our analysis was primarily based on the spirometry data obtained prior to bronchodilator use. The existing literature suggests that postbronchodilator spirometry may offer more precise predictions of mortality risk than prebronchodilator measurements. However, the discrepancies between the two sets of measurements are relatively minor, thus our findings are still considered valuable (Respirology 2020;25:401-09). We acknowledge this limitation and have discussed it in the discussion section (Page 20, Lines 383-390).

Changes in the text: Without modification.

Comment 2: *Second, the study's generalizability is limited to U.S. adults, and racial/ethnic differences in pulmonary function patterns may restrict applicability to other populations.*

Reply: Thank you for your valuable comment. We acknowledge the limitation regarding generalizability to populations outside U.S. adults and the potential impact of racial/ethnic differences on pulmonary function patterns. This has been addressed in the Discussion section to highlight this important consideration (Page 20, Lines 390-392).

Changes in the text: Without modification.

Comment 3: *Third, the cross-sectional nature of $FEV_{0.5}$/FVC measurements precludes investigating longitudinal changes in the ratio and their impact on health outcomes.*

Reply: Thank you for your insightful comment. Due to the absence of longitudinal data for the metric of $FEV_{0.5}$/FVC, we were unable to investigate the potential association between the temporal changes in $FEV_{0.5}$/FVC and respiratory health outcomes. This limitation has been clearly noted in the Discussion section (Page 20, Lines 397-400).

Changes in the text: Without modification.

Comment 4: *Additionally, unmeasured confounding factors (e.g., environmental exposures, medication use) could influence the observed associations.*

Reply: Thank you for your valuable comment. We have made every effort to adjust for covariates affecting all-cause mortality, including sex, age, race, body mass index, and

smoking status. However, there may still be unmeasured confounding factors influencing our results, such as environmental exposures (e.g., air pollution) and medication use (e.g., inhaled corticosteroids). (Environ Int. 2020;143:105974. Environ Int. 2020;142:105876. Am J Respir Crit Care Med. 2021;203:553-64. Am J Respir Crit Care Med. 2020;201:1508-16.) We acknowledge that these unmeasured confounders are likely to affect the findings within NHANES. Accordingly, we have added a description of these limitations in the Discussion section of the manuscript.

Changes in the text: We have modified our manuscript as advised (see Page 20, lines 392-397 in the revised manuscript).

Comment 5: *Finally, the biological mechanisms underlying the U-shaped relationship between $FEV_{0.5}$/FVC and mortality remain unclear, requiring further mechanistic studies to elucidate.*

Reply: Thank you for your valuable comment. We agree that the biological mechanisms underlying the U-shaped relationship between $FEV_{0.5}$/FVC and mortality are not yet fully understood. We have acknowledged this limitation and provided a detailed discussion with possible explanations in the Discussion section, highlighting the need for further mechanistic studies (Page 18, Lines 342-358). It is first necessary to distinguish between obstructive and restrictive ventilatory disorders in the context of varying pulmonary function states. In obstructive pulmonary diseases such as small airway obstruction syndrome, the reduction in expiratory flow due to airway blockage results in a decrease in $FEV_{0.5}$, while FVC remains relatively normal or is only

minimally reduced. This leads to a reduction in $FEV_{0.5}$/FVC. (Am J Respir Crit Care Med 2001;163:1256-76. Chest 1999;116:231-3.) In contrast, in restrictive lung diseases such as interstitial pneumonia, alveolar expansion is limited, resulting in a decrease in lung volume (both FVC and total lung capacity) with a smaller decrease in (or almost unchanged) $FEV_{0.5}$, leading to a normal or increased $FEV_{0.5}$/FVC. (Eur Respir Rev 2014;23:40-54.) Both obstructive and restrictive airway ventilation dysfunction impact the risk of all-cause mortality to varying degrees, forming the two ends of the U-shaped curve. Second, it is important to consider inter-individual variability. Significant heterogeneity exists in pulmonary function and airway responsiveness among individuals. This biological diversity may lead to a reduction in the risk of all-cause mortality within a specific range of $FEV_{0.5}$/FVC. Outside of this range, the risk of mortality increases. However, this phenomenon remains to be validated in further scientific research.

Changes in the text: Without modification.

Comment 6: *In the main text, the primary outcome was described as mortality, so I suggest the authors to indicate the outcomes and clinical research design of this study in the title.*

Reply: Thank you for your kind comments. We have revised the title to: "Association of $FEV_{0.5}$/FVC Ratio with All-cause Mortality in Adults: A Cohort Study". This explicitly highlights the mortality endpoint and cohort design.

Changes in the text: We have modified our manuscript as advised (see Page 1, lines 1-2 in the revised manuscript).

Comment 7: *In the abstract, the background needs to clarify the clinical or public health needs for this research focus, the methods need to describe how the* $FEV_{0.5}/FVC$ *data were measured and how the mortality and respiratory outcomes were measured, the results need to describe the sample characteristics, mortality rates, and overall respiratory outcomes, and report the effect size measures that linking* $FEV_{0.5}/FVC$ *ratios and death and other outcomes, and the conclusion needs more detailed comments for the implications of the findings.*

Reply: We sincerely appreciate your valuable suggestions for improving the abstract. As recommended, we have made the following revisions to address each point. In the **Background** section, we supplemented the clinical requirements for the new indicator $FEV_{0.5}/FVC$. In the **Methods** section, we would like to clarify that detailed descriptions of the measurement procedures for $FEV_{0.5}/FVC$, mortality, and respiratory outcomes are comprehensively presented in the Methods section of the manuscript. In the **Results** section, we have added the key sample characteristics, mortality rates, and primary respiratory outcomes data. Due to the word limit and the concise nature of the abstract, additional detailed results are presented comprehensively in the main Results section of the manuscript. In the **Conclusions** section, we have enhanced the clinical implications of the findings.

Changes in the text: We have modified our manuscript as advised (see Page 4, lines 59-61; Page 4-5, lines 78-85; Page 5, lines 86-89 in the revised manuscript).

Comment 8: *The current version of the introduction is confusing and inadequate. It remains unclear why the authors had this research focus. I suggest the authors to review the public health and clinical importance of respiratory diseases, the importance of identifying biomarkers associated with these health outcomes and mortality, and analyze the potential of $FEV_{0.5}$/FVC as a prognostic biomarker.*

Reply: Thank you for your kind comments. In response to the valuable comments of the reviewers, we have greatly strengthened the introduction in order to better express the research motivation and illustrate the potential of $FEV_{0.5}$/FVC as a biomarker (Page 7, Lines 112–120). Chronic respiratory diseases (CRDs), including COPD, asthma, pneumoconiosis, interstitial lung diseases, and sarcoidosis, impose a significant global disease burden. (EClinicalMedicine. 2023;59:101936. Lancet Respir Med. 2020;8:585-96. BMJ. 2020;368:m234.) Early diagnosis, clinical management, and prognostic assessment of CRDs rely on lung function testing; however, current lung function indicators inadequately capture early lesions and clinical features in the general population. The forced expiratory volume in 1 second (FEV_1)/forced vital capacity (FVC) ratio remains a key parameter widely used in respiratory health assessment and clinical trials. Recently, novel indices such as FEV_1/FEV_3, FEV_3/FEV_6, FEV_1/FEV_6, and $FEV_{0.75}$/FVC have shown promise across various scenarios. Notably, the $FEV_{0.75}$/FVC and $FEV_{0.5}$/FVC ratios have demonstrated efficacy in assessing asthma

control and wheeze impairment in preschool children; however, their prognostic value in adults has not been explored. To address this gap, we analyzed data from the National Health and Nutrition Examination Survey (NHANES) to investigate the association between $FEV_{0.5}$/FVC and respiratory health prognosis in adults, aiming to enhance pulmonary function assessments in high-risk populations.

Changes in the text: We have modified our manuscript as advised (see Page 7, Lines 112–120 in the revised manuscript).

Comment 9: *In the methods, please correctly describe the clinical research design, sampling of the NHANES studies, follow up procedures for the morality, and explain the assessment of respiratory health outcomes, cross-sectional or longitudinal follow up, and the statistics needs to describe the calculation of effect size measures such as OR and HR values.*

Reply: We sincerely appreciate your valuable suggestions for improving the Methods section. To better present the Methods section, we have not only addressed your specific suggestions but also optimized the overall structure of the section (Page 8-12, Line 140-235). The detailed revisions are outlined below for your kind review.

Regarding **Clinical Research Design and NHANES Sampling**, we have clarified cohort design and NHANES' stratified multistage sampling. Our data were obtained from NHANES, conducted by the National Center for Health Statistics (NCHS) under the U.S. Centers for Disease Control and Prevention (CDC). NHANES is a continuous, nationally representative survey employing a complex, multistage probability sampling

design with stratification, clustering, and oversampling of key demographic groups to assess the health and nutritional status of the civilian, non-institutionalized U.S. population. Data collection combines standardized in-home interviews, physical examinations, and laboratory tests performed in mobile examination centers. The NHANES protocol was approved by the NCHS Research Ethics Review Board. We analyzed data from two cycles—NHANES III (1988–1994) and 2007–2012—selected based on availability of lung function measurements alongside comprehensive demographic and health-related data.

Regarding **Outcomes**, we have explained the assessment of respiratory health outcomes. All-cause mortality was the primary endpoint. Mortality outcomes were ascertained by probabilistic linkage of NHANES participants to the National Death Index (NDI) using 12 identifiers—including social security number, date of birth, and sex—and verified by death certificates. Follow-up started at the baseline examination and ended on December 31, 2019, with survival time calculated in person-months. All-cause mortality was derived from the NHANES Linked Mortality File, which is maintained by the NCHS. The secondary outcomes were the risks of comorbidities and chronic respiratory symptoms. We selected eight comorbidities for analysis, including asthma, chronic bronchitis, emphysema, congestive heart failure, stroke, cancer, diabetes mellitus, and hypertension. Information regarding the presence of comorbidities was obtained from the participants using baseline questionnaire at NHANES enrollment. We also gathered data on four chronic respiratory symptoms, including chronic cough, chronic phlegm, wheezing, and dyspnea. Information

regarding chronic respiratory symptoms was obtained via baseline patient self-reporting.

Regarding **Statistical Analysis**, we sincerely appreciate the reviewer's insightful comment regarding the need to clarify the calculation of effect size measures. While we fully agree on the importance of transparent statistical methodology, we have chosen not to include the detailed computational formulas for HR and OR in the main text to maintain focus on the clinical implications of our findings.

However, to ensure full transparency, we would like to clarify here:

- Hazard Ratios (HRs) were calculated using Cox proportional hazards models, reflecting the mortality risk associated with $FEV_{0.5}$/FVC ratios over follow-up time.
- Odds Ratios (ORs) were derived from multivariable logistic regression, representing the odds of respiratory outcomes per $FEV_{0.5}$/FVC group change.

We believe this balance maintains readability while upholding methodological rigor, but we are happy to incorporate additional technical details if the editor deems it necessary.

Changes in the text: We have modified our manuscript as advised (see Page 8-12, Line 140-235 in the revised manuscript).

Comment 10: *The English language of the whole paper needs professional editing. For example, in the sentence "The study included participants aged ≥20 years who were not pregnant, had quality-controlled prebronchodilator lung function and mortality*

data, and had complete body measurements and mortality follow-up data." please change "aged ≥20 years" to "aged 20 years and older." The preposition "aged" is generally followed by a noun phrase, not an adverbial phrase. "Aged 20 years and older" is more grammatically correct.

Reply: We sincerely appreciate your valuable suggestions for improving the language quality of our manuscript. As recommended, we have conducted a thorough professional language editing of the entire paper, with particular attention to the grammatical issues you highlighted.

Changes in the text: We have modified our manuscript as advised (see Page 4, lines 65 and 69 in the revised manuscript).