Peer Review File

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Reviewer A

Comment 1. The subject is very relevant, and it seems that the data are good, but the manuscript has too many flaws. Style and Grammar are very poor, rendering crucial information on methodology and results difficult to understand.

Response: Thanks for your comments. We have invited Prof. Wei-jie Guan from Guangzhou Institute of Respiratory Health, First Affiliated Hospital of Guangzhou Medical University for the linguistic revision of the manuscript.

Comment 2. Although the authors state that sampling procedures are explained elsewhere, the reader should have a minimum of information so that he/she can understand what has been done on the present manuscript. That is not the case here, unfortunately. One example: the reader does not know what the authors mean by "Smoking": is there a threshold in pack-years? Only the current smokers are considered as " smoking"? Was previous smoking accounted for? There are many other examples.

Response: Thank you for your comment. We have revised the study design and participants, exposure assessment, and the covariates. Definitions of variables have been added in the main document and the supplementary material (E-Table 1).

1. Study design and participants

Between 2014 and 2019, we adopted a multistage, probability-based sampling strategy for COPD surveillance in six districts or counties of Guangdong province [22]. Briefly, residents aged ≥ 40 years living in the current surveillance point for at least 6 months were eligible for participation. Residents with cognitive defects, language or mental disorders, cancer, paraplegia, or were pregnant or breastfeeding were excluded. Data were collected during a consultation in a healthcare facility by trained staffs from the local health stations or community clinics. The study protocol

was approved by the ethics committee of the National Center for Chronic and Non-Communicable Disease Control and Prevention, China Center for Disease Control and Prevention in 2015 and in 2019. All participants had provided written informed consent. In our study, a total of 7418 and 5249 participants were included for analyzing the effects of occupation exposure to VGDF on chronic bronchitis and lung function, respectively (E-Figure 1). (Method-study design and participants)

2. Clinical assessments

Trained staffs conducted pre- and post-bronchodilator spirometry among all eligible participants by using commercial spirometers (MasterScreen Pneumo, Jaeger, Germany), in accordance with the international guidelines [3,23]. We obtained at least three technically acceptable and repeatable maneuvers for each participant. The highest values of forced expiratory volume in one second (FEV1), forced vital capacity (FVC), and maximal mid-expiratory flow (MMEF) were selected. Lung function values measured with post-bronchodilator spirometry were adopt in subsequent analysis.

Records of respiratory symptoms, including chronic cough and phlegm, were derived from the standardized questionnaire based on the Epidemiologic Standardization Project Questionnaire of the American Thoracic Society (ATS-DLD-78-A) [1]. Persistent cough denoted coughing on most days (≥ 4 days per week) for at least three months each year in the absence or presence of cold (participants answers to several items on coughing). Persistent phlegm denoted sputum production on most days (≥ 4 days per week) for at least three months each year in the absence or presence of cold (participants responding ‘yes’ to this question item). Respondents also reported the frequency of respiratory symptoms. Chronic bronchitis was defined as coughing up phlegm for at least three months in two consecutive years [25]. (Method-Clinical assessments)

3. Exposure assessment

A standardized questionnaire was used to ascertain occupational exposure to VGDF. Participants were requested to answer the occupational information including the job title, industry, and the duration of work, which were associated with occupational

exposure to VGDF. Participants exposed with any item of the VGDF for more than 1 year over their lifetime were considered occupationally exposed. All participants were divided into four groups: exposure to dust only, exposure to gas/vapor/fume only, dual exposure to dust and, gas/vapor/fume, and non-occupational exposure. (Method-Exposure assessment)

4. Covariates

We captured the following covariates from the questionnaire survey: age, sex (Male, female), height, education level (none+primary school education/middle school education or higher), marriage status (married/unmarried), region of residence (urban/rural), body-mass index (BMI) (underweight/normal/overweight/obese), smoking status (no/yes) and biomass fuel (no/yes). The type and definition of the exposure and covariates are shown in E-Table 1. (Method-covariates)

5. Definiton of the variables.

E-Table 1 Type and definition of the variable in the questionnaire.

Variable	Types of variables	Definition
Age[1-2]	Quantitative	Years of age; date of interview minus date of birth
Sex[1-2]	Qualitative	
Male		Male
Female		Female
Educational level[1-2]	Qualitative	
None+Primary school education		Without any education experience, primary school education
Middle school education or higher		Middle school education or higher
Marriage status[1-2]	Qualitative	
Unmarried		Unmarried
Married		Married
Region[1-2]	Qualitative	
Urban		Urban regions defined by the administrative regions in China
Rural		Rural regions defined by the administrative regions in China
Biomass fuel exposure[1]	Qualitative	
No		Not eligible for the definition of biomass fuel exposure
Yes		Household use of biomass fuels (including wood,

		grass, crop residues, and animal dung), or coal fuels (including coal, lignite, and kerosene) for cooking for more than 14 days a year, or heating throughout winter
Smoking status[1]	Qualitative	
No		Not smoke every day or occasionally
Yes		Having smoked every day or occasionally
Chronic bronchitis[1]	Qualitative	
No		Not eligible for the definition of chronic bronchitis.
Yes		Coughing up phlegm for at least three months in two consecutive years
Cough[1]	Qualitative	
No		Not eligible for the definition of cough
Yes		Coughing on most days (≥ 4 days per week) for at least three months each year in the absence or presence of cold (participants answers to several items on coughing)
Phlegm[1]	Qualitative	
No		Not eligible for the definition of phlegm
Yes		Sputum production on most days (≥ 4 days per week) for at least three months each year in the absence or presence of cold (participants responding 'yes' to this question item).
Dust	Qualitative	
No		No occupational exposure to dust, gas, vapor and fume
Yes		Participants exposed with dust for more than 1 year over their lifetime
Gas, vapor and fumes	Qualitative	
No		No occupational exposure to dust, gas, vapor and fume
Yes		Participants exposed with gas, vapor and fume for more than 1 year over their lifetime
dust and gas/vapor/fume	Qualitative	
No		No occupational exposure to dust, gas, vapor and fume
Yes		Participants exposed with any one of the dust, gas, vapor and fume for more than 1 year over their lifetime

Comment 3.Did the authors record how long the exposures had gone on? For how many hours a day? Previous exposure was recorded or only current one? That is crucial for a reasonable critical reading.

Response: We had asked the participants how long they worked on exposure work accurate to year, but did not specify how many hours a day.

Comment 4. Some of the findings yield statistically significant but biologically irrelevant results. For example, FEV1/FVC should not be treated as a continuous variable, and a difference of 1.05 does not say much about lung function impairment. MMEF is not a suitable parameter either. FEV1 is a very robust parameter, but the authors express it only in liters, which is improper once it is affected by anthropometric features, age, sex, etc. The reader should have access to % predicted values. That would be much more significant from a physiological standpoint. Examples regarding other parameters: a statistically significant difference of 40 mL in FVC is hard to interpret on physiological grounds among thousands of individuals.

Response: Thanks for your comments. In the reference of "Yang T, et al. China Pulmonary Health Study Group. Association of fine particulate matter air pollution and its constituents with lung function: The China Pulmonary Health study. Environ Int. 2021 Nov;156:106707.", the authors studied the effects of the fine particulate matter air pollution on multiple constituents of lung function indices including FEV_1/FVC (%), FEV_1 (mL), FVC (mL), MMEF (mL), etc.

In this study, all lung function parameters have been treated as continuous variables. The unit of FEV_1/FVC, FEV_1, FVC and MMEF was expressed as %, mL, mL and mL, respectively. Adopting the predictive value instead of the absolute values of lung function parameters could help exclude the bias of age, sex and height between individuals (all these are the core components for calculating the predicted value for the lung function parameters). However, the predicted values of lung function could not be accurately extrapolated among women <145 cm and men <155 cm in height (the existing reference equations are all based on participants with the

height that fell out of these ranges), which would result in an excessive loss of 680 participants. After joint discussion,

(1) We treated all lung function parameters as continuous variables. In addition, regression models were adjusted for age, sex and height.

(2) To clarify the results, we have revised the description of "lung function impairment" to "lower lung function" in the full text.

(3) Although it should be acknowledged that MMEF is not an optimal small airway parameter, it remains to be one of the most widely used parameter that is derived from spirometry (the "gold standard" measurement for defining airflow limitation). MMEF has been adopted as the key parameter to indicate small airway obstruction in the large population-based surveys (see reference: 1. Niu Y, et al. China Pulmonary Health Study Group. Long-Term Ozone Exposure and Small Airway Dysfunction: The China Pulmonary Health (CPH) Study. Am J Respir Crit Care Med. 2022 Feb 15;205(4):450-458; 2. Xiao D,et al China Pulmonary Health Study Group. Prevalence and risk factors of small airway dysfunction, and association with smoking, in China: findings from a national cross-sectional study. Lancet Respir Med. 2020 Nov;8(11):1081-1093.) These studies suggested small airway obstruction (partly evidenced by the decreased MMEF) as a strong predictor of chronic airway obstructive diseases. In addition, there is a scarcity of validated parameter apart from MMEF which could reliably reflect small airway obstruction in clinical practice.

In light of this, We have decided to retain MMEF in the analysis. We have also added the comments in the Discussion section as the limitation of our interpretation: "Although MMEF is not an optimal small airway parameter, it remains the most widely used parameter derived from spirometry and could indicate small airway obstruction in most large-scale population-based studies[1-2].". (Discussion-Para 5-Line 9~12)

Comment 5. Tables should be clearer and less extensive.

Response: Thank you for your suggestion. The tables in the supplementary material have been revised and streamlined from 18 tables to 7 tables, making it clearer and less extensive. Please refer to the details in the Supplementary Material.

Comment 6. From what I could grasp, the Discussion makes assumptions that do not follow the findings. The wording of the Discussion exaggerates the relevance of the findings. It is unreasonable to call minute differences of two weak parameters (see comment 4) "impaired lung function". Even if FEV1/FVC were a robust parameter, mean values are normal even in exposed subjects.
Response: Thank you for pointing this out. We have revised the wording to replace "lung function impairment" with "lower lung function " and have been more cautious in drawing the conclusions.

Reviewer B

Comment 1. Please merge tables for men and women and limit the number of models for each analysis.
Response: Thank you for your suggestion. The tables in the supplementary material have been revised and streamlined from 18 tables to 7 tables, making it clearer and less extensive. Please refer to the details in the Supplementary Material.

Comment 2. The amount of data and tables drowns the results the way it is organized now.
Response: As mentioned above, the tables in the supplementary material have been streamlined from 18 tables to 6 tables. Please refer to the details in the Supplementary Material.

Comment 3. Also figures could be merged (several smaller graphs in one figure).
Response: Thank you for your suggestion. We have merged 6 figures into 2 figures in the revised manuscript.

Reviewer C

Comment 1. Good and important study especially for companies that employ workers in polluted environments.

Response: Thanks for the reviewer's positive comments.

Comment 2. Study population were mainly middle aged adults, however, the authors reported that the population are young adults also they used a questionnaire adopted from International Study of Asthma and Allergies in Childhood.

Response: We are sorry for the erroneously citing the references in this manuscript. We have revised the reference and the description as follows:

"Records of respiratory symptoms, including chronic cough and phlegm, were derived from the standardized questionnaire based on the Epidemiologic Standardization Project Questionnaire of the American Thoracic Society (ATS-DLD-78-A) [24]. Persistent cough denoted coughing on most days (≥ 4 days per week) for at least three months each year in the absence or presence of cold (participants answers to several items on coughing). Persistent phlegm denoted sputum production on most days (≥ 4 days per week) for at least three months each year in the absence or presence of cold (participants responding 'yes' to this question item). Respondents also reported the frequency of respiratory symptoms. Chronic bronchitis was defined as coughing up phlegm for at least three months in two consecutive years [25]." (Method-Clinical assessments-Para 2)

See reference: [24] Ferris BG. Epidemiology Standardization Project (American Thoracic Society). Am Rev Respir Dis. Dec 1978;118(6 Pt 2):1-120.

Comment 3. They concluded that Occupational exposure to VGDF is associated with impaired lung function, however, its not the case. The reduction was not clinically or statistically significant. It show only a trend with the exposure to gas, vapor and fumes only after adjusting for with the age, sex, height, education level, marriage status, region of residence, body-mass index, smoking status and biomass fuel.

Response: Thanks for your comment.

(1) Exposure subgroups: All participants were divided into four groups: 1) exposure to dust only, 2) exposure to gas/vapor/fume only, 3) dual exposure to dust/gas/vapor/fume, 4) non-occupational exposure.

In our study, We observed statistical significance in the reduction of FEV_1/FVC and MMEF among the population who were exposed to gas, vapor and fumes or VGDF. (Supplementary material-E-table 4).

(2) To conclude with caution, we revised the description as follows:

2.1 "VGDF exposure was associated with chronic bronchitis, respiratory symptoms and decreased lung function, suggesting that VGDF contributes to the pathogenesis and progression of COPD." (Abstract-Conclusion).

2.2 "Occupational exposure to VGDF is associated with a trend of decreased lung function in the whole population." (Main document-Conclusion-Line 3~4).

Reviewer D

Comment 1. On page 4, lines 52-54, “Only two studies…”, please specify what is the current knowledge on the association between VGDF and chronic bronchitis. These two studies were from ECRHS, but studies from other cohorts/countries also matter, such as:

1) LeVan TD, et al. Vapor, dust, and smoke exposure in relation to adult-onset asthma and chronic respiratory symptoms: the Singapore Chinese Health Study. American journal of epidemiology 2006;163(12):1118-28.

2) Alif SM, et al. Occupational exposure to pesticides are associated with fixed airflow obstruction in middle-age. Thorax 2017;72(11):990-97.

More importantly, can the authors justify briefly why the current results are inconsistent? A brief introduction on the VGDF exposure would be helpful to justify the investigation of the exposure.

Response: Thanks for your suggestion. We have included the aforementioned references and specified the current knowledge on the association between VGDF and

chronic bronchitis. In addition, we have demonstrated the significance of this study. Details have been described as follows:

(1) Several studies have analyzed the association between occupational exposures to VGDF and chronic bronchitis and its related respiratory symptoms based on the studies conducted in Europe [European Community Respiratory Health Survey (ECRHS)] Australia and Singapore [8-11]. However, these studies revealed inconsistent results. For instance, Sunyer et al [8] reported an association between occupational exposures to dust with chronic phlegm but not with chronic bronchitis, while Lytras et al [10] and LeVan et al [11] reported a positive association between mineral dust exposure and chronic bronchitis. (Introduction-Para 1-Line 9~16).

(2) Previous studies regarding the association between occupational exposure with chronic bronchitis, respiratory symptoms and lung function, mainly conducted in industrial groups with high levels of exposures [17,18]. This might have rendered these studies to have suffered from the healthy worker effect and selection bias (the affected workers would have to leave from the highly exposed jobs), which could have collectively resulted in the underestimation of the true risk [19,20]. Community-based studies recruiting the participants from the general population can help minimize the bias mentioned above, however, nearly all these studies have been conducted in Western countries. In addition, occupational exposure to VGDF may frequently co-exist in real-world scenarios. However, few studies have evaluated the association between dual exposure (dust plus gas/vapor/fumes) and respiratory symptoms and lung function in developing countries, including China [20]. (Introduction-Para 3)

Comment 2. It is unclear what the eligibility criteria are for the age of the participants. The introduction shows that the study aims to investigate the effects of VGDF on middle-aged and older adults, but this is not clearly stated in the methods section.

Response: Thank you for your comment. We have added the relevant information in the Method-Study design and participants-Line 3~4:

“Briefly, residents aged ≥ 40 years living in the current surveillance point for at least 6 months were eligible for participation.”

Comment 3. Can the authors specify the definitions of lung function impairment in the methods section? Were participants who underwent both pre- and post-bronchodilator spirometry included in the analyses of lung function impairment? When assessing the associations with lung impairment, were FEV1, FVC, and FEV1/FVC obtained after bronchodilator use? Please state clearly in both the method and results sections.

Response: We have added the information in the Method-Clinical assessments-Line 6~7: “The absolute values of lung function parameters, measured with post-bronchodilator spirometry, were adopted in subsequent analysis.”

We have revised “decreased lung function” or “lower lung function” instead of “lung function impairment” in the whole manuscript.

Comment 4. It is unclear how the questionnaires assess occupational exposure, as there are different questions to collect occupational information. In the discussion section, it is mentioned that a job exposure matrix (JEM) cannot be used due to the large sample size. However, some kinds of standardization or matrix should have been used. Have the exposure assessment questionnaires been previously validated? Was the duration of exposure taken into account? For example, is working in a VGDF-exposed industry for 1 month 20 years ago the same as working for 20 years until the study period? I would suggest including the relevant questionnaires/methods of defining exposures in the appendix for readers to refer to and add relevant discussions about potential bias caused by such definitions

Response: Thank you for your comment and advice.

(1) To clarify the concerns, we have revised Method-Exposure assessment and added the definition of the variables in E-Table 1 of the supplementary material.

1.1 Exposure assessment

A standardized questionnaire was used to ascertain occupational exposure to VGDF. Participants were requested to answer to the occupational information including the the job title, industry, and the duration of occupation which were associated with occupational exposure to VGDF. Participants with exposure to any item of VGDF for more than 1 year over their lifetime were considered as occupationally exposed. All participants were divided into four groups: exposure to dust only, exposure to gas/vapor/fume only, dual exposure to dust and, gas/vapor/fume, and non-occupational exposure.(Method-Exposure assessment)

1.2 Definition of the variables.

F-Table 1 Type and definition of the variable in the questionnaire.

Variable	Types of variables	Definition
Age[1-2]	Quantitative	Years of age; date of interview minus date of birth
Sex[1-2]	Qualitative	
Male		Male
Female		Female
Educational level[1-2]	Qualitative	
None+Primary school education		Without any education experience, primary school education
Middle school education or higher		Middle school education or higher
Marriage status[1-2]	Qualitative	
Unmarried		Unmarried
Married		Married
Region[1-2]	Qualitative	
Urban		Urban regions defined by the administrative regions in China
Rural		Rural regions defined by the administrative regions in China
Biomass fuel exposure[1]	Qualitative	
No		Not eligible for the definition of biomass fuel exposure
Yes		Household use of biomass fuels (including wood, grass, crop residues, and animal dung), or coal fuels (including coal, lignite, and kerosene) for cooking for more than 14 days a year, or heating throughout winter
Smoking status[1]	Qualitative	

No		Not smoke every day or occasionally
Yes		having smoked every day or occasionally
Chronic bronchitis[1]	Qualitative	
No		Not eligible for the definition of chronic bronchitis.
Yes		Coughing up phlegm for at least three months in two consecutive years
Cough[1]	Qualitative	
No		Not eligible for the definition of cough
Yes		Coughing on most days (≥ 4 days per week) for at least three months each year in the absence or presence of cold (participants answers to several items on coughing)
Phlegm[1]	Qualitative	
No		Not eligible for the definition of phlegm
Yes		Sputum production on most days (≥ 4 days per week) for at least three months each year in the absence or presence of cold (participants responding 'yes' to this question item).
Dust	Qualitative	
No		No occupational exposure to dust, gas, vapor and fume
Yes		Participants exposed with dust for more than 1 year over their lifetime
Gas, vapor and fumes	Qualitative	
No		No occupational exposure to dust, gas, vapor and fume
Yes		Participants exposed with gas, vapor and fume for more than 1 year over their lifetime
dust and gas/vapor/fume	Qualitative	
No		No occupational exposure to dust, gas, vapor and fume
Yes		Participants exposed with any one of the dust, gas, vapor and fume for more than 1 year over their lifetime

(2) Participants having worked with more than 1 year over their lifetime were considered as occupationally exposed. Owning to the small number of participants reporting chronic bronchitis and the relevant respiratory symptoms, our study will have more insufficient power to support subgroup analyses based on the duration of exposure. Therefore, the analyses might have biased the magnitude of association. we have also added the limitation in the discussions of manuscript:

“Third, owing to the small number of participants reporting chronic bronchitis and the relevant respiratory symptoms, we did not conduct any further subgroup analyses based on the duration of exposure. ” (Discussion-Para 5-Line 7~9)

Comment 5. Have dust and gas/vapor/fume been mutually adjusted in the models separately? Please consider conducting a sensitivity analysis for mutual adjustments. Please add the prevalences of symptoms in front of the ORs.

Response: “Participants with exposure to any item of VGDF for more than 1 year over their lifetime were considered as occupationally exposed. All participants were divided into four groups: exposure to dust only, exposure to gas/vapor/fume only, all exposure to dust, gas, vapor and fume, and non-occupational exposure.” (Method-Exposure assessment-Line 6-8).

According to the groups mentioned above, sensitivity analysis would not be necessary. The prevalence of symptoms is presented in Table 1.

Comment 6. As all associations were shown in males and females respectively, it would be important to state this clearly in the method. Also, please justify why the authors are interested in the sex difference. The stratified results are lengthy and are presented in tables for males and females. Can the authors perform a likelihood test to see if the associations of VGDF with chronic bronchitis and lung function impairment are modified by biological sex?

Response: We have added the relevant information in the Method and Results sections:

(1) “Because of the notable differences in occupational category and intensities between males and females in the same occupationally exposed industry, we performed a analysis stratified by sex to examine the differential effect of occupational exposure of VGDF on lung function. When statistically significant effect

was observed, a likelihood test was further performed." (Method-Statistical analysis-Para 2)

(2) Results:

2.1 "Detailed results are shown in E-Table 3. Likelihood test showed that the gender differences in the effects of dust exposure on phlegm, VGDF exposure on both cough and phlegm were not statistically significant (both P>0.05)." (Results-Association between VGDF and respiratory symptoms-Para 2-Line 6~8)

2.2 " Likelihood test showed that the gender differences in the effects of gas/vapor/fume exposure on MMEF were not statistically significant." (Results-Association between VGDF and lung function -Line 15~16)

Comment 7. Information on the frequency of respiratory symptoms was collected by questionnaires. Please consider performing additional analyses to assess whether the associations of VGDF with cough and phlegm are modified by different frequencies of these respiratory symptoms (i.e. chronic cough and/or chronic phlegm as usually defined in other studies).

Response: We asked the study participants in the questionnaire about the frequency of respiratory symptoms to determine whether the participants have chronic bronchitis, cough or phlegm. We asked whether they have cough or phlegm at least twice a day for more than 4 weeks, or whether they often coughed or phlegm when they got up. However, the frequencies of chronic bronchitis, cough or phlegm were not collected, we have added this part as the limitation:

"Second, the magnitude of association might have been biased by the self-reported exposure, respiratory symptoms and symptoms without frequencies." (Discussion-Para 5-Line 5~7)

Comment 8. Chronic bronchitis, respiratory symptoms, and spirometry data are associated with COPD. Could the authors consider performing analyses to explore the associations between VGDF and COPD when data are available?

Response: Thank you for your suggestion. In this study, we mainly focused on the effects of occupational exposure to dust, gas, vapor and fumes on chronic bronchitis and lung function. We will explore the associations between VGDF and COPD in the next step.

Comment 9. Page 7 lines 126-128, consider providing details of the "five stepwise model" in the appendix, and define "change materially".

Response: Thank you for your suggestion.

We have changed the number of the models from 5 to 3, the details of which have given in the revised manuscript (Method-statistical analysis-Para 1-Line 15-23):

"We performed three regression models by adjusting for different variables as follows:

Model 1: Occupational exposure to dust, gas/vapor/fume or dust/gas/vapor/fume;

Model 2: Model 1 further adjusted with the age, sex, education level, marriage status, region of residence;

Model 3: Model 2 further adjusted with the BMI, height, smoking status and biomass fuel.

Results were deemed materially changed when there was a transition (e.g. from significant to no significance, or the vice versa) in the direction of the associations of model 1 to model 3." (Method-statistical analysis-Para 1-Line 21-24):

Comment 10. The discussion could focus on the type of obstruction that is seen here, rather than just discussing lung function findings as impairment. Can you comment on whether the lung function impairment is just obstructive or a mixed type (see Dharmage SC , et al. Lifetime spirometry patterns of obstruction and restriction, and their risk factors and outcomes: a prospective cohort study. The Lancet Respiratory Medicine. 2023 Mar 1;11(3):273-82)? Given it is only the ratio but not the FVC that

is low, we may not be seen a more severe obstruction. Can you unpack your lung function findings more?

Response: Thanks for your advice. The type of airway obstruction did not completely match with any type of the lung function mentioned in the manuscript mentioned above (Dharmage SC, et al. Lifetime spirometry patterns of obstruction and restriction, and their risk factors and outcomes: a prospective cohort study. Lancet Respiratory Medicine. 2023 Mar 1;11(3):273-82).

Notably, our study has provided the evidence that occupational exposure to gas/vapor/fume or VGDF was significantly associated with small airway obstruction (partly evidenced by the low MMEF). It should be acknowledged that MMEF is not an optimal small airway parameter, it remains to be one of the most widely used parameter that is derived from spirometry (the "gold standard" measurement for defining airflow limitation). MMEF has been adopted as the key parameter to indicate small airway obstruction in the large population-based survey (see reference: 1. Niu Y, et al. China Pulmonary Health Study Group. Long-Term Ozone Exposure and Small Airway Dysfunction: The China Pulmonary Health (CPH) Study. Am J Respir Crit Care Med. 2022 Feb 15;205(4):450-458; 2. Xiao D, et al China Pulmonary Health Study Group. Prevalence and risk factors of small airway dysfunction, and association with smoking, in China: findings from a national cross-sectional study. Lancet Respir Med. 2020 Nov;8(11):1081-1093.) These studies suggested that small airway obstruction (e.g. decreased MMEF) was a strong predictor of chronic airway obstructive diseases.

We have revised the Discussion of the lung function findings as follows: "Previous studies have provided some evidence for an association between VGDF exposure and lower levels of lung function, but the findings remained contradictory. Several cross-sectional studies [35-37] and a longitudinal study [38] did not suggest an association between exposure to VGDF and accelerated lung function decline. A five-year follow-up study reported that fume exposure was associated with significantly decreased FEV1 among individuals with early-stage COPD [12]. These studies were conducted solely based on the young adults, patients with a known

diagnosis of COPD, a single industry or occupational category, or lung function parameters reflecting large airway disorders (decreased FEV1). By contrast, our study sought to address different questions. For instance, we were more concerned whether the occupational exposure to VGDF would affect the lung function in the general population. Second, we probed into the hypothesis whether the adverse effects of dual occupational exposure to dust and gas/vapor/fume on lung function would be synergistic. Third, we added MMEF as one of the important indices of lung function, which has been adopted as the key parameter to indicate small airway obstruction in the large population-based studies [39-40]. From the standpoint of the study design, our study has included the older general population from the community. These findings highlighted the role of VGDF exposure in small airway obstruction (partly evidenced by the decreased MMEF), resulting in the progression of chronic airway obstructive diseases such as COPD [41]. Our study was not designed to specifically address the plausible mechanisms how VGDF exposure could dampen the lung function. We speculated different mechanisms leading to airflow limitation related to different kinds of VGDF, depending on the biochemical pathways as well as the vapor and aerosol droplet size." (Discussion-Para 4)

Comment 11. On page 11, lines 214-217, "These findings indicated that the age, the duration of exposure…" is repeated on page 14, lines 266-269, "A more heterogenous characteristic of each occupational exposure…". Please rephrase and provide more details to discuss the results in comparison to other studies. This would be important to highlight the consistent findings and your novelty, as the authors have stated that most current studies are contradictory.

Response: Thanks for your comment. We have revised the discussion:

(1) "A number of population-based studies have reported the association between dust exposure and symptoms related to chronic bronchitis [26]. However, few studies have evaluated the association between chronic bronchitis and gas, vapor and fume, particularly dual exposure of dust and gas/vapor/fume. Our study has added substantially to the of evidence pertaining to the association between occupational

exposure to VGDF and chronic bronchitis. Similar to the finding of an earlier analysis in the cohort of ECRHS, there was no statistically significant association between occupational exposures to mineral dust and chronic bronchitis in young adults [9]. However, the latest cohort study of ECRHS showed an increased risk of chronic bronchitis associated with mineral dust exposure [10]. A positive association between the exposure to gas/vapor/fume and chronic bronchitis was not demonstrated in the latest cohort study of ECRHS [10], which was similar to the findings of our study. These indicated that social economic status including age [27], life exposure, residential area and education level might have collectively explained for the inconsistent findings across the studies. After adjusting for the age, sex, height, education level, marriage status, region of residence, body-mass index (BMI), smoking status and biomass fuel by using the PS algorithm, results of the occupational effects of dust or gas/vapor/fume did not change materially, rendering our results robust. A key research question of our study was whether the adverse effects of dual occupational exposure to dust and gas/vapor/fume would be synergistic. Indeed, based on the cross-sectional survey in Guangdong province, we have noted a higher risk of chronic bronchitis in participants with dual occupational exposure to VGDF when compared with those exposed to dust or gas/vapor/fume alone. The mechanisms pertaining to the effect of occupational exposure to VGDF on chronic bronchitis are less clear. VGDF are a heterogeneous category of exposures, which have been linked to various forms of pulmonary toxicity [28-30], for instance, the significant association between vanadium exposure and chronic bronchitis have been reported [28,30]. ” (Discussion-Para 2)

(2) ”Previous studies have provided some evidence for an association between VGDF exposure and lower levels of lung function, but the findings remained contradictory. Several cross-sectional studies [35-37] and a longitudinal study [37] did not suggest an association between exposure to VGDF and accelerated lung function decline. A five-year follow-up study reported that fume exposure was associated with significantly decreased FEV1 among individuals with early-stage COPD [12]. These studies were conducted solely based on the young adults, patients with a known

diagnosis of COPD, a single industry or occupational category, or lung function parameters reflecting large airway disorders (decreased FEV1). By contrast, our study sought to address different questions. For instance, we were more concerned whether the occupational exposure to VGDF would affect the lung function in the general population. Second, we probed into the hypothesis whether the adverse effects of dual occupational exposure to dust and gas/vapor/fume on lung function would be synergistic. Third, we added MMEF as one of the important indices of lung function, which has been adopted as the key parameter to indicate small airway obstruction in the large population-based studies [39-40]. From the standpoint of the study design, our study has included the older general population from the community. These findings highlighted the role of VGDF exposure in small airway obstruction (partly evidenced by the decreased MMEF), resulting in the progression of chronic airway obstructive diseases such as COPD [41]. Our study was not designed to specifically address the plausible mechanisms how VGDF exposure could dampen the lung function. We speculated different mechanisms leading to airflow limitation related to different kinds of VGDF, depending on the biochemical pathways as well as the vapor and aerosol droplet size." (Discussion-Para 4)

Comment 12. On page 14, lines 275-277, "…decreasing the statistical power to detect the associations in females", the small number of females may be one of the limitations, but I would suggest using statistical power as a limitation if there is no association, whereas the authors observed some associations in females.

Response: Thank you for your suggestion. We observed that the confidence intervals were wide, which might be associated with the small sample size. We have revamped this sentence in the revised manuscript:

"First, the prevalence of chronic bronchitis in females (0.77%) was relatively lower than in males (3.63%), therefore the confidence intervals of effect estimates for VGDF and chronic bronchitis were wide in females. " (Discussion-Para 5-Line 1~3)

Comment 13. In the abstract, “Results of sensitivity analysis did not…”, it is unclear what sensitivity analysis was conducted and what information this analysis provides.

Response: We have revised and added the description as follows:

“ We performed sensitivity analyses based on two methods of propensity score (PS) methods to evaluate the robustness of our results.” (Abstract-Method-Line 5~7). Details of the method and results have been provided in the main document of the revised manuscript.

Comment 14. On Page 4, lines 46-47, “Chronic bronchitis…core manifestation of COPD”, please add citations.

Response: Thank you for your suggestion. The citations have added in the revised manuscript:

4. Izquierdo-Alonso JL, Rodriguez-Gonzálezmoro JM, de Lucas-Ramos P, et al. Prevalence and characteristics of three clinical phenotypes of chronic obstructive pulmonary disease (COPD). Respir Med 2013;107(5):724-731.

Comment 15. Please add citations on page 4, lines 64-66, “However, few studies have evaluated.

Response: Thank you for your suggestion. The citations have been added in the revised manuscript.

21.Caillaud D, Lemoigne F, Carré P, et al. Association between occupational exposure and the clinical characteristics of COPD. BMC Public Health 2012;12:302.

Comment 16. On page 8, line 149, as the characteristics are not the same for the double exposure, it would be good to briefly mention which characteristics are similar.

Response: The characteristics for the dual occupation exposure have described in the revised manuscript:

“ Participants with VGDF were more likely to be males, living in rural areas and smoking. Apart from having a lower level of education, a normal BMI status, these participants also had a higher frequency of cough and phlegm with higher FVC, lower FEV1/FVC and lower MMEF (all P<0.05).” (Results-Baseline characteristics of the study participants-Line 8~11)

Comment 17. On page 9, lines 163-166, “After adjusting for covariates…”, this description is not accurate since exposure to dual exposure is associated with chronic bronchitis in models 1-4 at the conventional level at 0.05. Please rephrase.
Response: Regarding that dual exposure was not associated with chronic bronchitis in the final adjusted model (model 3) at the significance level of 0.05, we have decided to retain the previous description and deleted the sentence: “The association was robust based on the consistent results from Model 1 to Model 5” from the main text (Results-Association between VGDF and respiratory symptoms-Para 2- Line 6~7).

The sentence has been rephrased in the revised manuscript: “After adjusting for important covariates, exposure to dust was associated only with phlegm, while VGDF exposure was associated with both cough and phlegm in females. ”. (Results-Association between VGDF and respiratory symptoms-Para 2-Line 4~6)

Comment 18. On page 9, lines 170-173, “Compared with those without exposure to VGDF…”, while the effect estimates show the associations of exposure to gas/vapor/fumes instead of the exposure to VGDF. Please consider rewording.
Response: We have revamped as follows: “Compared with the reference group, the mean FEV1/FVC was 1.05 lower (95%CI: -1.85, -0.26, P=0.01 in Model 3), MMEF was 0.15 L/min lower (95%CI: -0.23, -0.07, P<0.001 in Model 3) in participants with occupational exposure to gas/vapor/fume (Figure 2, E-Table 4). ” (Results-Association between VGDF and lung function-Line 3~6)

Comment 19. Please refer to figures and tables in the order in which they appear in the main text

Response: Thank you for your suggestion. We have rearranged and merged the tables and figures in the revised manuscript.

Comment 20. On page 11, lines 205-206, "However, few studies have … as an important outcome". It is unclear what this sentence means. Please rephrase.
Response: According to your suggestion, we have reworded the sentence: "However, few studies have evaluated the association between chronic bronchitis and gas, vapor and fume, particularly dual exposure of dust and gas/vapor/fume.". (Discussion-Para2-Line 2-4)

Comment 21. On page 11, lines 217-219, "Positive associations between the exposure to gas, vapor, and fume …in the latest cohort study of ECRHS…", please add citations to specify which ECRHS study you referred to
Response: The citation of the reference have been added.
10.Lytras T, Kogevinas M, Kromhout H, et al. Occupational exposures and incidence of chronic bronchitis and related symptoms over two decades: the European Community Respiratory Health Survey. Occup Environ Med 2019;76(4):222-229.

Comment 22. On page 13, lines 247-250, "Although a cohort study from…lack of information on lung function decline…", if this study does not assess the association between VGDF and lung function decline, why did the authors put the comparison here?
Response: Thank you for your suggestion. We have removed this sentence from the revised manuscript.

Comment 23. On page 2, line 23, please spell out VGDF when it first appears (lines 20-21)
Response: We have added the abbreviation of VGDF when it first appeared:
"Chronic obstructive pulmonary disease is one of the leading causes of mortality worldwide, and therefore the identification of the modifiable risk factors for

accelerate disease progression has important significance, such as exposure to vapors, gases, dust and fumes (VGDF)" (Abstract-Background-Line 3)

Comment 24. In the Abstract section, lines 24-26 "a total of 7418 and 5249 participants were included", this is confusing, please reword and specify the meaning of these two numbers (those with data on symptoms, those with data on lung function)

Response: We have reworded in the revised manuscript.

(1) "A total of 7418 participants were included" (Abstract-Results-Line 1)

(2) " In this study, a total of 7418 and 5249 participants were included for analyzing the effects of occupation exposure to VGDF on chronic bronchitis and lung function, respectively (E-Figure 1)." (Methods-Study design and participants- 11~13)