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RESEARCH ARTICLE

The associations between air pollutant exposure and neutralizing antibody titers of an inactivated SARS-CoV-2 vaccine

Shaocheng Zhang[1] · Shu Chen[1] · Guangjun Xiao[1] · Mingcai Zhao[1] · Jia Li[1] · Wenjuan Dong[2] · Juan Hu[1] · Tianqi Yuan[3] · Yong Li[3] · Lianghua Liu[1]

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Abstract

Air pollution is a critical risk factor for the prevalence of COVID-19. However, few studies have focused on whether air pollution affects the efficacy of the SARS-CoV-2 vaccine. To better guide the knowledge surrounding this vaccination, we conducted a cross-section study to identify the relationships between air pollutant exposure and plasma neutralizing antibody (NAb) titers of an inactivated SARS-CoV-2 vaccine (Vero cell, CoronaVac, SINOVΛC, China). We recruited 239 healthcare workers aged 21–50 years who worked at Suining Central Hospital. Of these, 207 were included in this study, depending on vaccination date. The data regarding air pollutants were collected to calculate individual daily exposure dose (DED). The geometric mean of all six pollutant DEDs was applied to estimate the combined toxic effects ($DED_{complex}$). Then, the participants were divided into two groups based on the mean value of $DED_{complex}$. The median plasma NAb titer was 12.81 AU/mL, with 85.99% vaccine efficacy in healthcare workers against SARS-CoV-2. In exposure group, observations included lower plasma NAb titers (median: 11.13 AU/mL vs. 14.56 AU/mL), more peripheral counts of white blood cells and monocytes (mean: 6.71×10^9/L vs. 6.29×10^9/L and 0.49×10^9/L vs. 0.40×10^9/L, respectively), and a higher peripheral monocyte ratio (7.38% vs. 6.50%) as compared to the reference group. In addition, elevated air pollutant DEDs were associated with decreased plasma NAb titers. To our knowledge, this study is the first to report the relationship between air pollutant exposure and plasma NAb titers of the SARS-CoV-2 vaccine. This suggests that long-term exposure to air pollutants may inhibit plasma NAb expression by inducing chronic inflammation. Therefore, to achieve early herd immunity and hopefully curb the COVID-19 epidemic, vaccinations should be administered promptly to those eligible, and environmental factors should be considered as well.

Keywords Air pollutants · Combined toxic effects · Neutralizing antibody titer · Inactivated SARS-CoV-2 vaccine · Chronic inflammation · Healthcare workers

Shaocheng Zhang, Shu Chen and Guangjun Xiao contributed equally as co-first authors.

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✉ Shaocheng Zhang
Zinssercheung@163.com

[1] Department of Clinical Laboratory Medicine, Suining Central Hospital, 127 Deshengxi Rd., Suining 629000, Sichuan, People's Republic of China

[2] Department of Public Health Administration and Health Education, Suining Central Hospital, Suining 629000, Sichuan, People's Republic of China

[3] Maccura Biotechnology Co. Ltd., Chengdu 611731, Sichuan, People's Republic of China

Abbreviations

DED Daily exposure dose
NAb Neutralizing antibody

Introduction

Coronavirus disease 2019 (COVID-19), which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has spread rapidly in more than 230 countries and regions and now poses an unprecedented threat to public health and socio-economic security (Barouki et al. 2021; Chen et al. 2021; He et al. 2021; Zhang et al. 2021a). SARS-CoV-2 might be able to survive in wastewater and hospital ward air and may persist on surfaces such as masks, handles, cupboards, switches, and fuel gun nozzle for a long

period, which presents a big threat of infection for those in a variety of different occupations (Dargahi et al. 2021a; Dargahi et al. 2021b; Karami et al. 2021a; Karami et al. 2021b; Sarailoo et al. 2021; Vosoughi et al. 2021). The World Health Organization (WHO) reported that there were about 226.23 million confirmed cases of COVID-19 and more than 4.65 million deaths worldwide as of September 16, 2021 (WHO. 2021). Vaccination is considered an essential step to obtain herd immunity against COVID-19. At this point, about 5.63 billion vaccine doses have been administered around the world (Amanat and Krammer 2020; He et al. 2021; Hodgson et al. 2021; WHO. 2021). Mounting research has reported that the efficacies of different SARS-CoV-2 vaccines ranged from 62.1 to 95.0% (Al Kaabi et al. 2021; Baden et al. 2021; Logunov et al. 2021; Polack et al. 2020; Sadoff et al. 2021; Voysey et al. 2021). However, few studies have focused on whether air pollution affects the efficacy of the SARS-CoV-2 vaccine.

Air pollutants are the critical risk factors for respiratory infection and play a crucial role in the prevalence of COVID-19 (Fareed et al. 2020; Sarwar et al. 2021; Shakoor et al. 2020; Zhang et al. 2019a; Zhang et al. 2019b; Zhang et al. 2021c). Systematic retrospective analyses indicated that SARS-CoV-2 could adhere to air particulate matter (PM), while PM and NO_2 might make the important contributions to the prevalence and lethality of COVID-19 through up-regulation of angiotensin-converting enzyme 2 expression in respiratory cells (Copat et al. 2020; Paital and Agrawal 2020; Srivastava 2021). Air pollutants may inhibit viral clearance and promote viral spread by preventing macrophage uptake and elevating epithelial permeability (Woodby et al. 2021). Epidemiological studies have reported that the short-term toxic effects of air pollutants were significantly associated with COVID-19 cases, showing that per 10 μg/m^3 enhancement of $PM_{2.5}$, PM_{10}, O_3, and NO_2, the daily confirmed cases of COVID-19 will increase by 2.24%, 1.76%, 4.76%, and 6.94%, respectively (Zhang et al. 2021c; Zhu et al. 2020). In the event of long-term exposure, each 1 m^3 increase of $PM_{2.5}$ could increase the confirmed cases of COVID-19 by 12% (Travaglio et al. 2021). In terms of mortality, the long-term exposure effects of air pollutants have been highlighted previously, and the results suggested that a 1 μg/m^3 enhancement of $PM_{2.5}$ was associated with 1.4% (England), 0.76% (Mexico), and 8% (USA) increase in COVID-19 mortality, while a NO_2 increase by 1 μg/m^3 could increase COVID-19 mortality by 0.5% in England (Konstantinoudis et al. 2021; Lopez-Feldman et al. 2021; Wu et al. 2020). In total, air pollution may accelerate the risk of COVID-19 transmission and lethality (Fareed et al. 2020; Shahzad et al. 2020; Shahzad et al. 2021). Although the role of air pollutants in COVID-19 prevalence has previously been emphasized, the relationships between air pollutants and neutralizing antibody (NAb) titers of the SARS-CoV-2 vaccine remain unclear.

Environmental pollution poses a greater risk of dangerous COVID-19 re-bursting than SARS-CoV-2 spike (Paital and Das 2021). In addition, our previous studies have determined that children who lived in an e-waste area with serious air pollution had the lower vaccine antibody titers against diphtheria, hepatitis B, Japanese encephalitis, measles, mumps, pertussis, polio, rubella, and tetanus than children who lived in another reference area (Cong et al. 2018; Lin et al. 2017; Lin et al. 2016; Xu et al. 2015; Zhang et al. 2019a; Zheng et al. 2016). The current study aims to investigate the effects of air pollutants on SARS-CoV-2 vaccine efficacy, and we hypothesize that long-term exposure to air pollutants will inhibit vaccine NAb titers against SARS-CoV-2. To prove this hypothesis, we (i) calculated the daily exposure dose (DED) of air pollutants ($PM_{2.5}$, PM_{10}, SO_2, NO_2, O_3, and CO) and their combined effects, (ii) assessed chronic inflammatory levels and plasma NAb titers after SARS-CoV-2 vaccination, and (iii) estimated the relationships between air pollutants and NAb titers in healthcare workers.

Materials and methods

Study population

A total of 239 healthcare workers from the ages of 21–50 years old at Suining Central Hospital were recruited randomly in this cross-sectional study during the period of April 22–23, 2021. To rule out the impact of different vaccination dates, the present study ultimately included 207 healthcare workers who received the first and second doses of inactivated SARS-Cov-2 vaccine (Vero cell, CoronaVac, SINOVΛC, China) on February 8, 2021, and March 10, 2021, respectively. Until biological sampling, all participants were free of any known medical condition, and signed an informed consent. To collect the basic information on lifestyle, living environment, educational status, and household monthly income, a questionnaire was complete by all individuals through the Sojump network platform. This study was approved by the Medical Research Ethics Committee of Suining Central Hospital, China (LLSNCH20210012).

Sampling and laboratory measurements

All operations were performed according to the mustard of International Standardization Organization (ISO) 15189 quality and management. The following participant metrics were collected by trained nurses: general physical information, including height and weight, and fasting cubital vein blood sampling. EDTA anticoagulant (2 mL) blood was applied to analyze the peripheral inflammatory cells and heparin sodium anticoagulant (5 mL) blood was used to separate plasma by centrifugation at 3500 rpm for 5 min at room temperature.

After this, the remainder of the blood and plasma was aliquoted and stored at −80°C.

Peripheral white blood cell (WBC) counts, monocyte counts, and the ratios of monocytes were tested by an automatic hematology analyzer (Sysmex XN-9000, Japan) within 1 h of sampling. Plasma was applied to measure NAb titers and assess health status. This included aspartate aminotransferase (AST), alanine aminotransferase (ALT), total protein, albumin, total bilirubinuric, direct bilirubinuric, total cholesterol, triglycerides, high-density lipoprotein–cholesterol (HDL-C), low-density lipoprotein–cholesterol (LDL-C), apolipoprotein A1, apolipoprotein B, urea, creatinine, and cystatin C. All health biomarkers were analyzed by an automatic biochemical analyzer (Hitachi LST 7600, Japan), and NAb titers were tested by an automatic chemiluminescence immunoassay analyzer (Maccura i 3000, China).

Exposure assessment

Four stations in Suining (85.04 km^2 area, http://stjj.suining.gov.cn/tjnj) monitor air pollutant concentrations ($PM_{2.5}$, PM_{10}, SO_2, NO_2, O_3, and CO), ensuring the individual activity radius of all participants less than 40 km from the nearest station, which is the threshold of monitoring station air pollutant data for assessing individual exposure (Bowe et al. 2017; Wang et al. 2020). Air pollutant data was released through the national real-time urban air quality platform (http://106.37.208.233:20035/), and collected to calculate individual air pollutant DED using a modified formula: $DED_i = C_i \times$ inhalation rate (IR) × individual weight/reference weight (Wang et al. 2020; Zheng et al. 2016). In this formula, C_i is the median concentration of pollutant i ($PM_{2.5}$, PM_{10}, SO_2, NO_2, O_3, and CO). IR was estimated by parameters of the adult, and the reference weights for adult males and females were 60 kg and 51 kg, respectively (Table S1) (Zheng et al. 2016). The assessment method of individual outdoor exposure time was described in our previous study in detail (Zhang et al. 2019a). In addition, we also estimated the DED of combined toxic effects ($DED_{complex}$) using the geometric mean of all six pollutant DEDs. Then, we divided all participants into two groups based on $DED_{complex}$ mean. The reference group was defined as $DED_{complex} \leq 0.8$ mg/day, and the exposure group was defined as $DED_{complex} > 0.8$ mg/day.

Statistical analysis

Mean ± standard deviation (SD) or median interquartile range (IQR) was used to depict data depending on the distribution characteristics, which were estimated by the Kolmogorov–Smirnov test. Logarithmic transformation was conducted to approximate and normalize the data distribution in plasma NAb titers. As expected, group differences were determined by the independent-sample *t*-test or the Mann-Whitney *U* test. The seasonal distribution characteristics of air pollutants were analyzed by the Kruskal-Wallis test. The Spearman rank correlation test was performed to identify associated confounders of air pollutant DEDs. In addition, multivariable-adjusted linear regression models were applied to assess the dose-effect relationships between air pollutant DEDs and plasma NAb titers. Covariates included gender, age, height, daily cigarette smoking, daily alcohol drinking, window opening frequency, distance between residence and road, educational status, and household monthly income (Cong et al. 2018; Zhang et al. 2019a). SPSS (version 22.0; IBM, USA) and GraphPad Prism (version 8.0; GraphPad, CA) were applied to analyze data and edit figures, respectively. $P < 0.05$ was statistically significant and was defined in a two-tailed test.

Results and discussion

General characteristics of the study population

There were 207 healthcare workers recruited in this cross-sectional study (Table S2). The gender ratio (male/female) was 69/138, and the median age was 31 years. The median of height and weight was 1.62 m and 56 kg, respectively. Most participants had no history of cigarette smoking (86.96%) or alcohol drinking (70.53%), spent more time (>2 h) outdoor per day (43.96%), lived far away (> 100 m) from the road (47.83%), or had a relatively lower income (below 10,000 yuan per month, 48.79%). In terms of health status, the median concentrations of AST, ALT, total bilirubinuric, direct bilirubinuric, triglycerides, and creatinine were found to be 21U/L, 14 U/L, 7.7 μmol/L, 2.2 μmol/L, 1.32 mmol/L, and 60 μmol/L, respectively. The mean concentrations of total protein, albumin, total cholesterol, HDL-C, LDL-C, apolipoprotein A1, apolipoprotein B, urea, and cystatin C were found to be 79.38 g/L, 48.47 g/L, 4.67 mmol/L, 1.23 mmol/L, 2.5 mmol/L, 1.56 g/L, 0.78 g/L, 5.36 mmol/L, and 0.76 mg/L, respectively.

Air pollutant DEDs and the associated factors

The annual mean concentrations of air pollutants were found to be 29.77 μg/m^3 ($PM_{2.5}$), 50.93 μg/m^3 (PM_{10}), 8.62 μg/m^3 (SO_2), 20.50 μg/m^3 (NO_2), 61.79 μg/m^3 (O_3), and 602.98 μg/m^3 (CO) (Figure 1 and Table S3). These results suggested that the air quality in Suining is better than in other cities, including Chengdu, Chongqing, Mianyang, and Fuling in the Sichuan Basin (Huang et al. 2020; Qiao et al. 2019; Wang et al. 2018; Wang et al. 2020; Zhang et al. 2021b). This difference might be attributed to the relatively low industrial status and small traffic flow in Suining. In addition, the concentration of air pollutants in Suining showed a seasonal difference, indicating that air pollution was severe in winter and low in summer (all

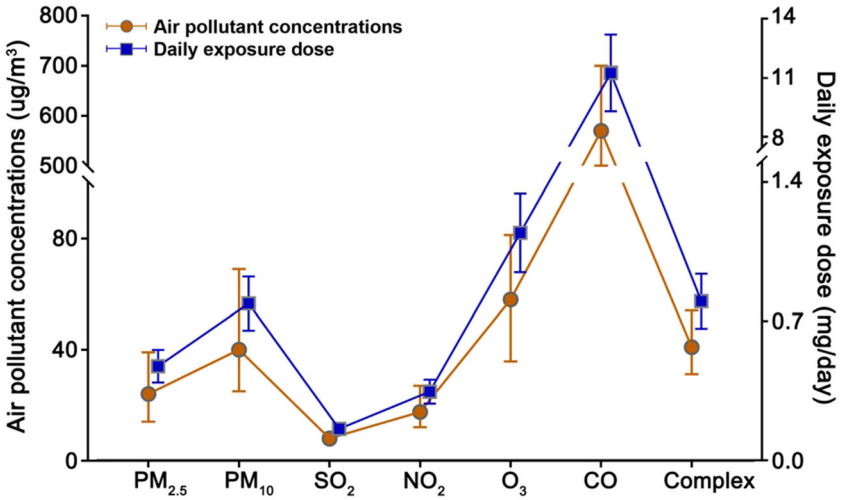

Fig. 1 Distribution characteristics of air pollutant concentrations and daily exposure doses

$P < 0.01$) (Table S3). The seasonal characteristics were consistent with previous studies (Wang et al. 2018; Wang et al. 2020; Zhang et al. 2021b).

The mean levels of air pollutant DEDs were found to be 0.47 mg/day ($DED_{PM2.5}$), 0.79 mg/day (DED_{PM10}), 0.16 mg/day (DED_{SO2}), 0.35 mg/day (DED_{NO2}), 1.14 mg/day (DED_{O3}), 11.25 mg/day (DED_{CO}), and 0.80 mg/day ($DED_{Complex}$) (Figure 1). Spearman rank correlation test was performed to identify whether there were confounders associated with air pollutant DEDs and indicated that air pollutant DEDs were correlated with height and unhealthy lifestyle (including cigarette smoking and alcohol consumption), whereas not associated with living environment, educational status, and household monthly income. For example, $DED_{PM2.5}$ was found to be positively associated with height, daily cigarette smoking, and daily alcohol consumption ($r_s = 0.652$, $r_s = 0.264$, and $r_s = 0.366$, respectively, all $P < 0.01$) (Table S4). Our previous studies determined that apart from lifestyle, the variables of living environment, parental educational status, and family socio-economic status were associated with pollution exposure levels in children (Lu et al. 2018; Zhang et al. 2019a). This difference may result from the idea that there is a higher environmental susceptibility in children than adults (Wild and Kleinjans 2003; Zhang et al. 2014). Collectively, unhealthy lifestyles could increase the risk of exposure to air pollutants, which had been highlighted.

Peripheral inflammatory status

Peripheral leukocytes play a crucial immune-regulatory role in systemic inflammation, and monocytes are chronic inflammatory biomarkers (Chabot-Richards and George 2014; So et al. 2021; Zhang et al. 2019a). Air pollution exposure could induce immunodysregulation and the systemic inflammatory response that involves monocytes and neutrophils (Calderon-Garciduenas et al. 2009; Xu et al. 2013). Group difference analysis showed in the exposure group, the peripheral counts of WBCs and monocytes were higher than in the reference group, accompanied by a higher ratio of monocytes in the exposure group (mean: 6.71×10^9/L vs. 6.29×10^9/L, 0.49×10^9/L vs. 0.40×10^9/L, and 7.38% vs. 6.50%, respectively, all $P < 0.05$) (Figure 2). Although there was no significant correlation between air pollution and peripheral leukocyte counts in disease models, mounting literature has suggested that air pollutant exposure ($PM_{2.5}$, PM_{10}, NO_2, black carbon, and sulfate) could increase peripheral counts of WBCs, monocytes, and neutrophils in healthy human (Dabass et al. 2018; Rich et al. 2012; Verheyen et al. 2021; Zhang et al. 2019a). This cross-sectional study was conducted in healthcare workers and suggested that the increased peripheral counts of WBCs, monocytes, and monocyte ratio in the exposure group was consistent with previous studies in healthy population. In total, this study indicated that long-term air pollutant exposure induced chronic inflammation in healthcare workers.

Plasma NAb titers and the relationships with air pollutant DEDs

The median plasma NAb titer was 12.81 AU/mL, and 85.99% ($n = 178$) of the participants exceeded or equaled 6 AU/mL, which was the cutoff value provided by the manufacturer. This suggests an 85.99% vaccine efficacy in healthcare workers against SARS-CoV-2. In addition, plasma NAb titers of the participants were lower in the exposed group than in the reference group (median: 11.13 AU/mL vs. 14.56 AU/mL, $P < 0.05$) (Figure 3). Recently, a phase 3 clinical trial reported that inactivated whole-virion SARS-CoV-2 vaccine (CoronaVac, SINOVΛC, China) has shown 83.5% efficacy in Turkey (Tanriover et al. 2021). Other studies have also indicated that the efficacies of different SARS-CoV-2 vaccines ranged from 62.1 to 95.0% (Al Kaabi et al. 2021;

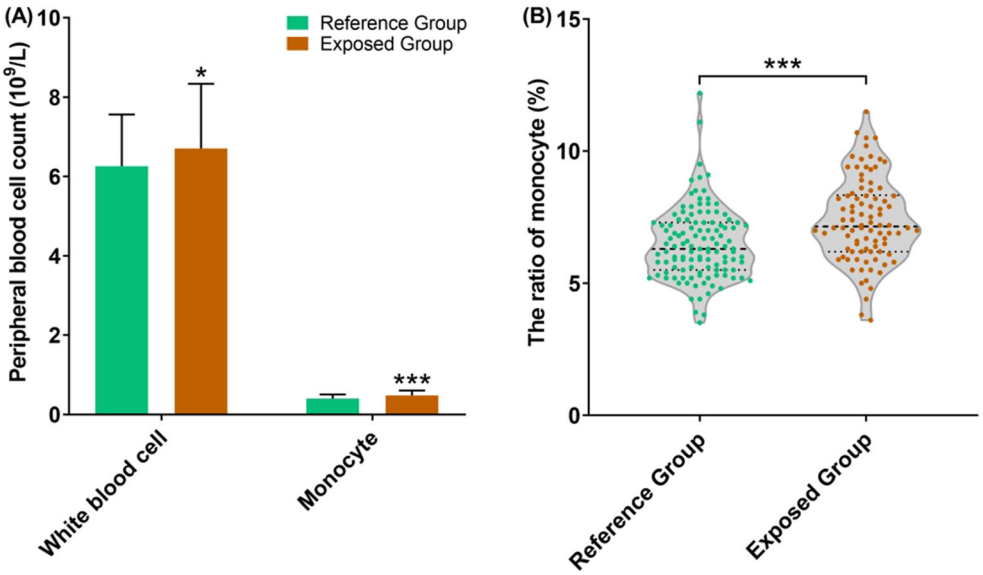

Fig. 2 Group differences of peripheral cell counts and monocyte ratio. Data are analyzed by independent-sample *t*-test, $^{*}P < 0.05$, $^{***}P < 0.001$

Baden et al. 2021; Logunov et al. 2021; Polack et al. 2020; Sadoff et al. 2021; Voysey et al. 2021). Although this study was performed in a specific group of healthcare workers, which differs from the vaccine types and race of participants in previous studies, the high efficacy of the inactivated SARS-Cov-2 vaccine (Vero cell, CoronaVac, SINOVΛC, China) is emphasized in the present study.

Our previous studies were performed in an e-waste recycling area where the air pollution was severe have suggested that environmental pollutant exposure could suppress vaccine antibody titers against diphtheria, hepatitis B, Japanese encephalitis, measles, mumps, pertussis, polio, rubella, and tetanus in children (Cong et al. 2018; Lin et al. 2017; Lin et al. 2016; Xu et al. 2015; Zhang et al. 2019a; Zheng et al. 2016). In addition, Paital and Das (2021) indicated that environmental pollution poses a greater danger of COVID-19 re-bursting than the SARS-CoV-2 spike. Therefore, we determined the relationships between air pollutant DEDs and plasma NAb titers by using the multivariable-adjusted linear regression model (Figure 4). Covariates were adjusted and included gender, age, height, daily cigarette smoking, daily alcohol consumption, window opening frequency, distance between residence and road, educational status, and monthly household income. The regression analyses indicated that air pollutant DEDs were significantly and negatively associated with plasma NAb titers [B (95% CI): −0.809 (−1.600, −0.019) for $PM_{2.5}$, −0.486 (−0.960, −0.011) for PM_{10}, −2.427 (−4.800, −0.055) for SO_2, −1.139 (−2.211, −0.068) for NO_2, −0.335 (−0.662, −0.008) for O_3, −0.034 (−0.067, −0.001) for CO, and −0.485 (−0.954, −0016) for combined toxic effects, all $P < 0.05$], which suggested that with each 1 mg/day DED increment of $PM_{2.5}$, PM_{10}, SO_2, NO_2, O_3, CO, and combined toxic effects, the logarithmic transformation of plasma NAb titers will decrease by 0.809 units, 0.486 units, 2.427 units, 1.139 units, 0.335 units, 0.034 units, and 0.485 units, respectively. Indeed, the results of the present study were consistent with those of previous studies, which highlighted that long-term exposure to environmental pollutants could inhibit the expression of the vaccine antibody in humans (Lin et al. 2017; Lin et al. 2016; Xu et al. 2015). Previous literature has indicated that environmental pollution posed a dangerous risk of COVID-19 epidemic re-bursting, preventive measures, such as mask-wearing and cleaning surfaces with 70% ethanol spray, are essential to limit infection (Paital 2020; Paital and Das 2021). Of course, to achieve early herd immunity and

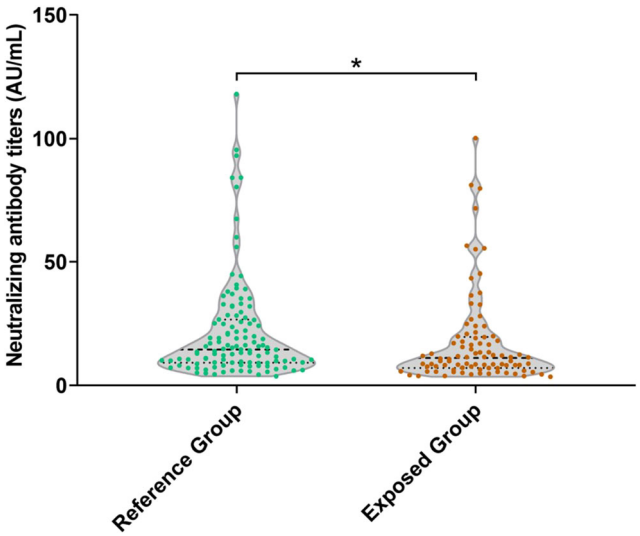

Fig. 3 Distribution characteristic of plasma NAb titers. NAb, neutralizing antibody; data are analyzed by the Mann-Whitney *U* test; $^{*}P < 0.05$

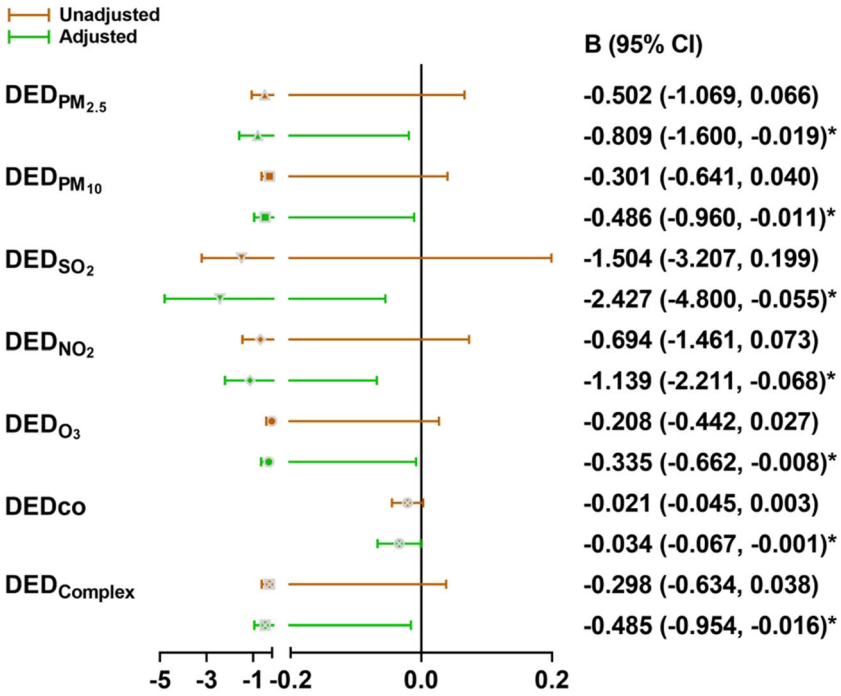

Fig. 4 Associations between air pollutant DEDs and plasma NAb titers. B, unstandardized coefficient; CI, confidence interval; NAb, neutralizing antibody; DED, daily exposure dose; adjusted for gender, age, height, daily cigarette smoking, daily alcohol consumption, window opening frequency, distance between residence and road, educational status, and monthly household income; *$P < 0.05$

stop the COVID-19 epidemic, vaccinations should be administered promptly, and environmental factors should be considered as well.

Several limitations of this cross-sectional study need to be noted. The sample size was small, and the only participants recruited were healthcare workers, which might limit the relationships of air pollutant DEDs and plasma NAb titers. However, as described in previous studies, our results emphasized that chronic environmental pollutant exposure inhibits the expression of the vaccine antibody in humans (Lin et al. 2017; Lin et al. 2016; Xu et al. 2015). In addition, an individual special residential address for each participant was not registered, but all participants were healthcare workers with the same place of work and live in Suining (85.04 km^2 area). This ensured that the activity radius of all participants was less than 40 km from the nearest station, which is the threshold of monitoring station air pollutant data for assessing individual exposure (Bowe et al. 2017; Wang et al. 2020).

Conclusion

In summary, we conducted a cross-sectional study to estimate the relationship between air pollutant exposure and plasma NAb titers of an inactivated SARS-CoV-2 (Vero cell, CoronaVac, SINOVΛC, China) vaccination. The results indicated that the median plasma NAb titer is 12.81 AU/mL, with 85.99% vaccine efficacy in healthcare workers against SARS-CoV-2. In addition, we observed increased incidence of chronic inflammatory status and decreased plasma NAb titers in the air pollutant exposure group. Moreover, elevated air pollutant DEDs were found to be associated with decreased plasma NAb titers. Collectively, our results support the hypothesis that long-term exposure to air pollutants may inhibit plasma NAb expression by inducing chronic inflammation. Therefore, to obtain herd immunity against SARS-CoV-2 infection and to stop the COVID-19 pandemic, local air pollution should be considered as a factor in future vaccination programs.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11356-021-16786-y.

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Author contribution Shaocheng Zhang designed the study, searched the literature, supervised data acquisition, revised the manuscript, and funded the study. Shu Chen and Guangjun Xiao worked for sampling, questionnaire collection, data analysis, and wrote the manuscript. Mingcai Zhao and Jia Li contributed equally to the work for sampling collections and experiment implementation. Wenjuan Dong, Juan Hu, and Lianghua Liu assisted in sampling and questionnaire collection. Tianqi Yuan and Yong Li helped in the process of the experiment for techniques.

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Data availability All data generated or analyzed are included in this published article and supplement.

Declarations

Ethical approval This study was approved by the Medical Research Ethics Committee of Suining Central Hospital, China (LLSNCH20210012).

Consent to participate and consent for publication All participants signed an informed consent, and all health data was handled anonymously in this study.

Competing interests The authors declare no competing interests.

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