Title

Air Pollution, Non-Pharmaceutical Interventions Policy, Vaccination and Coronavirus Disease 2019 (Covid-19) and Epidemiology of Lung and Upper Aerodigestive Tract Cancers

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Air Pollution, Non-Pharmaceutical Interventions Policy, Vaccination and Coronavirus Disease 2019 (Covid-19) and Epidemiology of Lung and Upper Aerodigestive Tract Cancers

A dissertation submitted in partial satisfaction of the requirements for the degree Doctor of Philosophy in Epidemiology

by

Fang Fang

2022

ABSTRACT OF THE DISSERTATION

Air Pollution, Non-Pharmaceutical Interventions Policy, Vaccination and Coronavirus Disease 2019 (COVID-19) and Epidemiology of Lung and Upper Aerodigestive Tract Cancers

by

Fang Fang

Doctor of Philosophy in Epidemiology

University of California, Los Angeles, 2022

Professor Zuo-Feng Zhang, Chair

Background: The original Ph.D. dissertation proposal was to study $PM_{2.5}$ and lung and UADT cancers, however, due to COVID-19 pandemic, we have added epidemiological studies of COVID-19 and still studied $PM_{2.5}$ and risk of lung and UADT cancers. Long-term exposure to fine particulate matter ($PM_{2.5}$) is an established risk factor for many adverse health outcomes via different mechanisms, and thus predisposes individuals and populations to elevated risks of both infectious and chronic health outcomes. Previous studies reported the association between $PM_{2.5}$ exposure and COVID-19 outcomes based on arbitrarily cut-off points. This study investigated this association during the first two surges of the pandemic and examined whether non-pharmacologic prevention initiatives might intervene this association. In addition, though

vaccines against SARS-CoV-2 were safe and effective, its community-wide impacts on reducing COVID-19 incidence and mortality corresponding to the predominant strain in the population have not yet been studied. Lastly, we aim to confirm the association between $PM_{2.5}$ and lung cancer susceptibility in Los Angeles, as well as addressing whether $PM_{2.5}$ is associated with UADT cancers susceptibility, which have been understudied.

Objective and Specific Aims: We aimed to evaluate the association between ambient $PM_{2.5}$ exposure and COVID-19 incidence and lung and UADT cancer susceptibility. The specific aims were: (1) to estimate the association between long-term exposure to ambient $PM_{2.5}$, facemask mandates, stay home orders and COVID-19 incidence in the United States during the first two surges; (2) to estimate the association between SARS-CoV-2 vaccines coverage and COVID-19 incidence and mortality in the United States during the Alpha, Delta, and Omicron predominance; and (3) to estimate the association between long-term exposure to ambient and indoor $PM_{2.5}$ and lung and UADT cancers susceptibility.

Study Design and Population: For Specific Aims 1 and 2, we employed a nation-wide ecologic study design, including more than 3,000 counties in the US. Analyses were conducted to estimate the associations between ambient $PM_{2.5}$, non-pharmacologic prevention initiatives, including facemask mandates and stay-home policies, and vaccination coverage at the county-level and COVID-19 incidence and mortality. The study utilized publicly available data. In Specific Aim 3, we aimed to estimate the association between air pollution and susceptibility of lung and UADT cancers, using a population-based case-control study in the Los Angeles County. The study included 577 lung cancer cases, 565 UADT cancers cases, and 983 controls after applying exclusion criteria.

Statistical Methods: For Specific Aim 1, we fit negative binomial models to assess COVID-19 incidence in association with $PM_{2.5}$ and policies during the first two surges of SARS-CoV-2 pandemic, as of September 12th, 2020. Stratified analyses by facemask policy and stay home policy were also performed. For Specific Aim 2, generalized estimating equations were used to estimate associations between US county-level cumulative complete vaccination rates and booster distribution and the daily change in county-wide COVID-19 risks and mortality during Alpha (April 23rd – July 2nd, 2021), Delta (July 3rd – December 1st, 2021) and Omicron (December 2nd, 2021 – March 25th, 2022) predominance. For both Aims, models were adjusted for potential confounders at both county and state level. A 2-week lag and a 4-week lag were introduced to assess vaccination rates impact on incidence and mortality, respectively. For Specific Aim 3, unconditional logistic regressions were applied to estimate the association between air pollution, including ambient $PM_{2.5}$ one-year before diagnosis, exposure to household air pollution, and an air pollution index, and lung and UADT cancers' susceptibility, adjusting for potential confounders.

Results: For Aim 1, after adjusting for county-level and state-level potential confounders, each 1-$\mu g/m^3$ increase in annual average concentration of $PM_{2.5}$ exposure was associated with an increase in COVID-19 risk (relative risk (RR) = 1.0756, 95% CI: 1.0376, 1.1149). Facemask mandates and stay home policies were inversely associated with COVID-19 with adjusted RRs of 0.8466 (95% CI: 0.7598, 0.9432) and 0.9193 (95% CI: 0.8021, 1.0537), respectively. The associations between $PM_{2.5}$ and COVID-19 were consistent among counties with or without preventive policies. For Aim 2, among 3,073 counties in 48 states, the average county population complete vaccination rates of all age groups were 50.79% as of March 11th, 2022. Each percentage increase in vaccination rates was associated with reduction of 4% (RR = 0.9607, 95%

CI: 0.9553, 0.9661) and 3% (RR = 0.9694, 95% CI: 0.9653, 0.9736) in county-wide COVID-19 cases and mortality, respectively, when Alpha was the dominant variant and after adjusting for potential confounders. The associations between county-level vaccine rates and COVID-19 incidence diminished during the Delta (RR = 0.9988, 95% CI: 0.9964, 1.0011) and Omicron (RR = 0.9969, 95% CI: 0.9919, 1.0019) predominance. Vaccination coverage was associated with slightly decreased COVID-19 mortality (RR = 0.9934, 95% CI: 0.9889, 0.9980) when Delta was the most prevalent strain, but with a marginal increase in COVID-19 mortality (RR = 1.0061, 95% CI: 1.0022, 1.0101) when Omicron was circulating. During the Omicron predominance, each percent increase in people receiving a booster shot was associated with reduction of 6% (RR = 0.9356, 95% CI: 0.9235, 0.9479) and 4% (RR = 0.9595, 95% CI: 0.9431, 0.9761) in COVID-19 incidence and mortality in the community, respectively. For Specific Aim 3, each 1-$\mu g/m^3$ increase in ambient $PM_{2.5}$ one-year before diagnosis was associated with elevated risks in lung (odds ratio (OR) = 1.02, 95% CI: 0.98, 1.06) and UADT (OR = 1.04, 95% CI: 1.00, 1.09) cancers susceptibility, adjusting potential confounding factors.

Conclusions and public health implications: These results add evidence to the associations between $PM_{2.5}$ with COVID-19 incidence and with lung and UADT cancers susceptibility. Thus, our results underscore the health hazards associated with increased ambient $PM_{2.5}$ and may be informative for policymaking and program planning for continuing to improve air quality. Moreover, the non-pharmacologic prevention initiatives and increasing vaccination coverage are shown to be effective in reducing COVID-19 incidence and mortality during different outbreaks of the SARS-CoV-2 variants, indicating both NPIs and vaccination are essential decisions in better preparation for the next surge of COVID-19 and even for the next emerging pandemic in the future.

The dissertation of Fang Fang is approved.

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University of California, Los Angeles

2022

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Chapter 3 is a work in preparation for submission and its previous version is available on medRxiv [2]. Dr. Zuo-Feng Zhang conceptualized and supervised the project. Dr. Zuo-Feng Zhang and I developed the methods. I obtained the data, conducted the analyses, and wrote the original manuscript. Drs. John David Clemens, Timothy F. Brewer and Zuo-Feng Zhang provided insightful feedbacks on the analyses and edited the draft. All authors reviewed and revised the manuscript for critical content.

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CHPATER 1. INTRODUCTION AND BACKGROUND

1.1 Coronavirus Disease 2019 (COVID-19)

1.1.1 Overview

Coronavirus Disease 2019 (COVID-19) is a human-to-human transmissible disease caused by the SARS-CoV-2 virus and was first discovered in Wuhan, China in December 2019 [3]. On March 11th, 2020, the World Health Organization (WHO) declared COVID-19 as a global pandemic [4]. Major modes of transmission include direct, indirect, or close contact with infectious respiratory fluid, airborne, and fomite [5, 6]. Once infected, the viral structural spike (S) protein of SARS-CoV-2 binds to the angiotensin-converting enzyme 2 (ACE2) receptor of the target cells, including nasal and bronchial epithelial cells [7]. The progression of the infection leads to endothelial barrier disruption, dysfunctional alveolar-capillary oxygen transmission, and impaired oxygen diffusion capacity and further triggers the viral inflammatory responses [8]. COVID-19 infection may cause respiratory symptoms, such as cough, shortness of breath or difficulty breathing, and congestion or runny nose, fever or chills, fatigue, muscle or body aches, new loss of taste or smell, or digestive symptoms, such as vomiting or diarrhea [9]. While most people have mild symptoms and can self-recover [10], severe symptoms, and even death, can be developed, especially among groups at high risk, including older adults, people with medical conditions, and pregnant or recently pregnant people [11].

1.1.2 COVID-19 in the United States

COVID-19 was the third leading cause of death, after heart disease and cancer, for two consecutive years from 2020 to 2021 [12]. As of May 27th, 2022, COVID-19 has caused 83,712,396 infections and has claimed 1,001,313 lives in the United States. The excess deaths since February 1st, 2020, were estimated to be 1,124,728. There were roughly 5 major surges in

the United States. The cut-off dates for each surge were May 28th, 2020, September 12th, 2020, July 2nd, 2021, and December 1st, 2021 [13]. The majority cases during the latter two surges were attributable to the Delta (B.1.617.2) variant [14] and the Omicron (B.1.1.529, BA.1, BA.1.1, BA.2 or BA.3) variant [15], respectively, which are classified as the Variants of Concern by the United States Centers for Disease Control and Prevention (CDC) [16].

1.2 Lung Cancer

1.2.1 Global Burden of Lung Cancer

According to the WHO 2020 GLOBOCAN, lung cancer was estimated to be the second most common cancer diagnosed, following breast cancer, and the most common cause of death from cancer. Over 65% of both new lung cancer cases and deaths were males, among whom lung cancer was the most common cancer diagnosed and the leading death due to cancer, while it was the third most common cancer and the second leading cancer mortality among females. In 2020, more than 2 million incident cases of lung cancer, accounting for 11.4% of all cancer diagnosis, were diagnosed and the high fatality rate pushed the death toll to over 1.7 million, contributing to 18% of deaths due to cancer, globally [17]. The GLOBOCAN estimates were similar to those reported by epidemiological studies [18].

Lung cancer is known to have high mortality and poor survival. To assess cancer survival, the CONCORD-3 study utilized information from 322 population-based cancer registries in 71 countries and territories from 2000 to 2014 and estimated the age-standardized 5-year net survival of different cancer types. For most countries, the age-standardized 5-year survival was between 10-20%, while higher survival rates were observed in more developed areas. Japan had

the highest survival rates at 32.9%. Other than regional disparity in lung cancer survival, temporal improvement of survival has also been observed. Even though the trend of lung cancer survival has been leveled off in recent years, the improved 5-year survival rates from 2010 to 2014 have been observed in 21 countries, comparing to the rates between 1995 and 1999. Moreover, such survival rate increased by more than 10% in China and Korea. The regional discrepancy and temporal survival change not only reflected the result of clinical practices and health care efficiency, but also might be due to other issues, such as screening availability, overdiagnosis, and better follow up of certain registries [19].

1.2.2 Lung Cancer in the United States

Similar to the global lung cancer pattern, lung cancer is among the top cancers and poses a heavy burden in the United States. Lung cancer is the 3rd most common cancer and the leading cause of cancer death, accounting for 235,760 (12%) of newly diagnosed cancer and 131,880 (22%) of cancer deaths in 2022. The trend of incidence and mortality in the US have been declining in recent decades. Male has higher risks of developing and dying from lung cancer than females. The 5-year relative survival from 2012 to 2018 in the US was 22.9% [20] and the US had the fourth highest survival rate in the world [19]. In general, cancer survival rates decrease as stage at diagnosis advances. In the case of lung cancer, the 5-year relative survival with diagnosis at localized stage was 61.2%, comparing to the survival rate of 7.0% for those diagnosed at distant stage. Unfortunately, due to the current practice, more than half (55%) of lung cancer were diagnosed at distant stage [20]. However, due to the implication of lung cancer screening in 2013, which is annual screening for lung with low-dose computed tomography in previous or current smokers [21], we will expect lung cancer to be diagnosed at earlier stages in coming years. As a result, we might expect the 5-year relative survival to increase in the US.

1.2.3 Histological Types of Lung Cancer

Lung cancer could be broadly classified as small cell lung cancer, non-small cell lung cancer, and some other less common subtypes. Among all these subtypes, non-small cell lung cancer makes up of about 80% to 85% lung cancer cases and could be further defined as adenocarcinoma (40% of cases), squamous cell carcinoma (25% to 30% cases), large cell carcinoma (10% to 15% cases), and other less common carcinoma types, based on the cell where the tumor originated [22].

Squamous cell carcinoma used to be the most prevalent subtype in males. In recent years, the incidence of squamous cell carcinoma and the one of adenocarcinoma were converging and nowadays in many countries, including the US, adenocarcinoma surpassed squamous cell carcinoma and became the most common subtype in males. Meanwhile, adenocarcinoma remained the most common subtype of lung cancer in females. Since adenocarcinoma is also the most common subtypes of lung cancer among nonsmokers, other factors besides smoking attribute to the development of adenocarcinoma [23, 24].

In addition, shift of smoking pattern and tobacco manufacturing also explain the trends of lung cancer subtypes. Women started smoking later than men. As a result, while the trends of overall lung cancer and squamous cell carcinoma are decreasing in men, such trends are increasing in women. Application of filter lead to deeper inhalation and a more peripheral distribution of smoke in the lung. Therefore, more cancer at peripheral sites, such as adenocarcinoma would be observed than central tumors, such as squamous cell carcinoma [25]. Composition of tobacco products also shifted from polycyclic aromatic hydrocarbons (PAHs), which induces squamous cell carcinoma, to tobacco-specific N-nitrosamines, which stimulates the development of adenocarcinoma [26]. Although smoking increases risks of all subtypes of lung cancer, the risk

of squamous cell carcinoma increases more rapidly after starting smoking than the risk of adenocarcinoma. Similarly, after smoking cessation, the risk of squamous cell carcinoma also decreases more rapidly than the one of adenocarcinoma [27, 28].

1.2.4 Risk Factors for Lung Cancer

As previously mentioned, both the trends of lung cancer, which reflect the patterns of tobacco consumption, and the increasing risk of all subtypes of lung cancer due to smoking indicate that tobacco is a major risk factor for lung cancer. The adverse health effects, including lung cancer, of tobacco smoking have been thoroughly studied since the publication of the 1964 Surgeon General Report on smoking and health [29, 30]. Tobacco smoke not only include smoking any type of cigarette, but also cigar smoking and pipe smoking [31, 32]. As the leading risk factor for lung cancer development, it was estimated to account for 90% of lung cancer cases [24] and 80% of lung cancer deaths [31]. The longer duration and greater intensity further increase lung cancer risks [26].

Among non-smokers, exposure to environmental tobacco smoking and radon may account for the majority of lung cancer cases in the US, while indoor air pollution still plays a role in less developed countries, where coal or solid fuels are used for cooking and heating [33]. Other environmental exposure, such as ambient air pollution, radiation and asbestos, and certain occupational group, including coal gasification, coke production, iron and steel founding, aluminum production, painting and rubber production industry, are associated with elevated lung cancer risks [34].

1.3 Upper Aerodigestive Tract Cancers

1.3.1 Overview

Upper aerodigestive tract cancers (UADTs) include head and neck cancer (HNC) and esophageal cancer. HNC indicates all cancers occurring in the nasal and oral cavities, such as oral cavity, nasopharynx, oropharynx, hypopharynx, larynx, paranasal sinuses and nasal cavity, and salivary glands [35].

1.3.2 Global Burden of Upper Aerodigestive Tract Cancers

Although each HNC sites accounts for small number of cases, combining all these subsites makes HNC the 6th most common cancer and the 7th most common cause of death from cancer in the world, equivalent to 931,931 new HNC diagnoses and 467,119 HNC deaths for both sexes in 2020. Males have a higher risk of developing HNC, accounting for 75% of incident cases and HNC mortality [17]. Other than sex, the heterogeneous risk and mortality of HNC are also observed among countries and among different cancer sites. The cancer of lip and oral cavity had the highest risks at 4.0 cases per 100,000 people, followed by laryngeal cancer and pharyngeal cancers, and the nasopharyngeal had the lowest incident rate at 1.2 cases per 100,000 people. Two thirds of HNC cases were in developing countries. Especially, the Indian subcontinent shared a great burden of cancers of the lip and oral cavity [36]. The estimated survival for HNC was about 49% based on the GLOBOCAN 2018 estimation. The global trends of both HNC incidence and mortality increases, with the exception of the US, where a decreasing mortality rate was observed [36].

Esophageal cancer, including squamous cell carcinoma and adenocarcinoma, had a similar profile of global incidence and mortality as HNC. There were 604,100 estimated incident cases

and 544,076 mortality due to esophageal cancer in both sexes. Though esophageal cancer was ranked the 8th most common cancer and the 6th most common cancer deaths, the uneven sex distribution was again observed in esophageal cancer. About 70% incident cases and esophageal cancer mortality occurred in men [17]. Based on the CONCORD-3 study, the 5-year net survival of esophageal cancer was between 10% to 30% in most countries. There were 12 countries with the 5-year survival more than 20%, including Japan, where the highest survival of 36% was observed. Comparing to the period of 1995 to 1999, the 5-year net survivals during 2010 to 2014 increased by at least 4% in 17 countries, whereas Korea experienced the greatest improvement in survival at 12.5% [19].

1.3.3 Upper Aerodigestive Tract Cancers in the United States

According to the Surveillance, Epidemiology, and End Results (SEER) data, HNC is the 10th most common cancer diagnosed, accounting for 66,470 cases after combining the cancer of oral cavity and pharynx and laryngeal cancer, in 2022. Consistent with the global HNC patters, HNC is more common in males, who have 2.7 times and 4.9 times risks in oral cavity and pharyngeal cancer and in laryngeal cancer comparing to females, respectively [37, 38]. More than 80% HNC cases in the US occurred in the oral cavity and pharynx. The incidence and mortality trends have leveled off since 1992 [38], because the declining incidences of oral cavity and hypopharyngeal cancers have been cancelled out by the rising incidence of oropharyngeal cancer, especially among population under age of 45 [39]. Half (50%) cases were diagnosed at regional stage, where the 5-year relative survival was 69.0% and the overall survival was 68.0% from 2012 to 2018 [38]. Cancer of larynx has displayed declining trends in both incidence and mortality since 1992. More than half (52%) cases were diagnosed at localized stage, where the 5-year relative survival was 78.3%. However, since the 5-year relative survival for both regional and distant

stage were lower than the ones of oral and pharyngeal cancers, laryngeal cancers had a lower overall 5-year relative survival at 61.0%. Unlike lung cancer and oral and pharyngeal cancers, women with laryngeal cancer had poorer prognosis than men [37].

Even though esophageal cancer is classified as one of the UADT cancers, it does show a different pattern than HNCs. Esophageal cancer is not a common cancer type in the US, accounting for 20,640 cancer diagnosis in 2022, and even rarer in females. The 5-year relative survival rate was 20.6% during the 2012 to 2018 period, which was similar to the one of lung cancer during the same period. Although half cases were diagnosed at localized or regional stages, the 5-year relative survivals for these stages were lower than the ones of lung cancer and the 5-year relative survival for distant stage of esophageal cancer was 5.7%, which was comparable to the one of lung cancer with metastasis [40].

1.3.4 Histological Types of Upper Aerodigestive Tract Cancers

Most HNCs occur in the oral and nasal cavities, where the lining are epithelial cells, and therefore the histological types are squamous cell carcinoma, accounting for 90% of HNC cases [36]. The exception is cancer originated from the salivary glands, which contain many different cell types. Thus, the histological types of cancer of salivary glands are very diverse. However, such cancer is rare in the US [41]. Esophagus is a muscular tube connecting pharynx and stomach. Though four consistent layers, including adventitia, muscle, submucosa, and mucosa, are found along the esophagus [42], the composition of cell types alters gradually from the proximal part to the distal part of the organ. The upper part of esophagus, which is also known as the cervical esophagus, consists of striated muscle and the distal esophagus contains smooth muscles [43]. While the squamous cell carcinoma distributes evenly in the upper and middle third parts of the esophagus, the majority of adenocarcinoma occurs at the lower third of the

esophagus [44]. Though squamous cell carcinoma has higher burden globally, the incidence of adenocarcinoma exceeds the one of squamous cell carcinoma and becomes the predominant subtypes in certain countries, including the US. Men have higher incidence for both subtypes, but the gender disparity is more pronounced in adenocarcinoma [45]. In addition, while squamous cell carcinoma is more common among blacks, whites have higher incidence of adenocarcinoma [46].

1.3.5 Risk Factors for Upper Aerodigestive Tract Cancers

Both smoked and smokeless tobacco products increase the risk of HNC [36] and both intensity and duration are important measurements for the risk of HNC [39]. About three quarters of HNC cases could be attributable to tobacco and alcohol use [35, 47]. Though exposing to either of the risk factors increases the risk of HNC, more than multiplicative interaction has been observed and simultaneous alcohol and tobacco use poses a larger threat, especially for oral and pharyngeal cancers [47]. Sustained infection caused by certain strains of human papillomavirus (HPV), such as HPV-16 and HPV-18, further stimulates carcinogenesis [36]. Increase intake of fruit and vegetable and reduced consumption of red meat might have a protective association with HNC [48], while consumption of salted fish, hot spices, and certain processed food, which containing nitroso compounds and volatile nitrosamines, is associated with elevated HNC risks [35]. Heavy bacterial load resulted from poor oral hygiene, exposure to radiation, including ultraviolet light, and chronic irritation to the lining of the mouth would also increase the risk of HNC [49]. Due to the heterogeneity of cancer site, there are specific risk factors for different sites. For example, Epstein-Barr virus is an important risk factor for nasopharyngeal carcinoma, but not for other HNC sites. Last but not least, even with effective local therapy, HNC patients

are at higher risks of second primary cancer at the upper aerodigestive tracts due to the dense lymph systems around the region [36].

Other than tobacco use and radiotherapy among breast cancer survivors, two subtypes of esophageal cancer have distinct sets of risk factors. Chronic irritation and inflammation are important cause for squamous cell carcinoma. Such irritation could be caused by tobacco smoking and substantial alcohol intake, which accounts for 90% of squamous cell carcinoma cases in the world. Similar to HNC, synergic effects of two exposures have been reported. Chronic irritation could be also caused by medical conditions such as achalasia, esophageal diverticuli, tylosis, Plummer-Vinson syndrome and esophageal injury due to frequent consumption of extremely hot beverages and ingestion of lye or other caustic fluids. Adenocarcinoma displays a different profile for risk factors. Barrett's esophagus, reflux, and obesity increase the risk of adenocarcinoma, while these risk factors are not associated with squamous cell carcinoma [50].

1.4 Fine Particulate Matter

1.4.1 Overview

Fine particulate matter (particles with aerodynamic diameter equal to or less than 2.5 μm in diameter, $PM_{2.5}$) may affect disease via a variety of mechanisms such as altering immune response, increasing oxidative stress, causing inflammatory injury, inducing mutagenicity, and introducing respiratory tract damage [51-53].

Both size and components of PM matter. Particles between 5 and 10 μm in diameter are likely to deposit in the trachea bronchial tree. Those from 1 to 5 μm could travel down to the respiratory

bronchioles and the alveoli where gas exchange occurs. These particles can affect gas exchange and even penetrate the lung and enter blood stream. Particles less than 1 μm behave similarly to gas molecules. Composition of PM also varies due to the pollution sources, ranging from inorganic chemicals to biological components. Some of these chemicals, such as heavy metals and polycyclic aromatic hydrocarbons, are carcinogenic. The adverse health effects of PM include lung cancer, respiratory symptoms, cardiovascular disease, preterm birth, low-birth weight, and emergency and hospital admission, have been established [54].

1.4.2 Ambient Particulate Matter

In 2013, the WHO has categorized both ambient air pollution and particulate matters (PM) in ambient air pollution as known carcinogen to humans. Particularly, clear associations between PM and lung cancer have been reported by various studies. Air pollution is regarded as the most widespread environmental carcinogen [55]. Moreover, government interventions, such as restricting the pollution industry and enforced vehicle emission test, are required to reduce air pollution level. In 2015, over 4 million deaths and over 283,000 deaths due to lung cancer could be attributable to PM. In the US, ambient PM is the 6th leading risk factor for deaths, which accounts for over 88,000 deaths [56]. Major sources of ambient air pollution include emission of motor vehicles, industrial processes, and power generation.

The annual mean of the WHO guideline for $PM_{2.5}$ is 5 μg/m^3 and the 24-hour mean is 15 μg/m^3 [57]. In 2005, the WHO estimated that about 89% of the world's population live in areas where annual $PM_{2.5}$ mean concentration exceeded 10 μg/m^3, the WHO guideline at that time [58]. The $PM_{2.5}$ pollution was more severe among middle-income countries such as China and India, especially around urban areas resulted from industrialization and increasing number of vehicles on roads [59].

1.5 Gaps in Literature

Detailed description of literature review and gaps in literature will be presented in the following chapters with each of the aims. Table 1-1 provides an overview of current literature in related topics. Briefly, timely evidence on the association between long-term exposure to air pollution, especially $PM_{2.5}$, and COVID-19 incidence is accumulating in the US and in Europe, however based on arbitrary cut-off points of the pandemic. With the progression of COVID-19, more extensive data would allow us to examine whether COVID-19 incidence was associated with long-term exposure to $PM_{2.5}$ during each surge of the pandemic and whether it might be modified by the implementation of preventive interventions, such as facemask mandates or stay home policies.

While vaccine efficiency was well studied at individual level, this study fills in the gap of the impact of vaccination on community-wide SARS-CoV-2 cases and COVID-19 mortality and addresses the impacts of vaccination within the entire community not just among those vaccinated. Moreover, it is worth examining whether and by how such impact might differ corresponding to different dominant strains in the community, especially in the light of vaccine waning and different breakthrough rate for each variant.

Though studies tried to investigate that association between air pollution and lung cancer risk or mortality, the results are somewhat inconsistent among studies, not to mention the magnitude, suggested by the large I^2 value of 53.0% for $PM_{2.5}$ [60]. Moreover, most of these studies covered population across a variety of geographic regions and over different periods of time, so that the source of emission and the levels of exposure might be different. Especially, the composition of

PM, which may be associated with different health effects, could change overtime or in different geographic regions. Hence, due to the heterogeneity of the association, it might not be appropriate to simply apply these findings to other populations. Limited evidence was available on the association between ambient air pollution and UADT cancers and most of these studies were underpowered. To our knowledge, this is the first study to examine the associations between ambient $PM_{2.5}$ and lung and UADT cancers susceptibility utilizing population-based data in Los Angeles with the availability of individual-level confounders and addressing the indoor air pollution at the same time.

1.6 Hypotheses and Specific Aims

Above-mentioned gaps in literature were addressed using a nation-wide ecologic study and a population-based case-control study with three specific aims listed below.

Specific Aim 1. To estimate the association between long-term exposure to ambient $PM_{2.5}$, facemask mandates, stay home orders and reported incident COVID-19 cases, based on the surveillance case definitions by the CDC [61], in the United States during the first two surges.

Specific Aim 1.1. To estimate the association between long-term exposure to ambient PM2.5, and reported COVID-19 cases in the United States during the first two surges by state implementation of facemask mandates and stay home policies.

Hypothesis 1. US county-level reported COVID-19 incidence is positively associated with long-term exposure with ambient $PM_{2.5}$, but inversely associated with state-level non-pharmacologic prevention initiatives (NPIs), such as facemasks mandates or stay home policies.

Hypothesis 2. The associations between long-term exposure to ambient PM2.5 and reported COVID-19 cases in the United States during the first two surges differ by the status of facemask mandates or stay home orders.

Specific Aim 2. To estimate the association between SARS-CoV-2 vaccines coverage and reported COVID-19 cases and mortality in the United States during the Alpha, Delta, and Omicron predominance

Specific Aim 2.1. To estimate the association between proportion of booster uptake and reported COVID-19 cases and mortality in the United States during the Omicron predominance.

Hypothesis 2. County-level SARS-CoV-2 vaccines coverage is associated with reduced COVID-19 incidence and mortality.

Hypothesis 2.1. The protective associations between county-level SARS-CoV-2 vaccines coverage and COVID-19 incidence and mortality diminish overtime.

Hypothesis 2.2. The protective associations between county-level SARS-CoV-2 vaccines coverage and COVID-19 incidence and mortality vary by the most dominant strain in the US.

Hypothesis 2.3. Increased county-level SARS-CoV-2 booster uptake in the population is associated with reduced COVID-19 incidence and mortality.

Specific Aim 3. To estimate the association between long-term exposure to ambient and indoor $PM_{2.5}$ and lung and UADT cancers susceptibility using a population-based case-control study in Los Angeles.

Hypothesis: Exposure to either long-term ambient $PM_{2.5}$ or indoor air pollution is associated with increased susceptibility of lung and UADT cancers.

CHAPTER 2. LONG-TERM EXPOSURE TO $PM_{2.5}$, FACEMASK MANDATES, STAY HOME ORDERS AND COVID-19 INCIDENCE IN THE UNITED STATES

2.1 Introduction

As of September 12th, 2020, COVID-19 has infected 6,353,677 people in the United States [13]. To avoid the human-to-human transmission of the pathogen, the US Centers for Disease Control and Prevention (CDC) recommends social distancing, face masking, and good hygiene practices [62]. Each state also implements different policies in order to slow down the spread of the disease [63]. A meta-analysis including 21 studies showed the efficacy of face masks in preventing respiratory virus transmission. The protective effect of facemask use against respiratory virus infection was 64% and a 47% risk reduction was observed among non-healthcare workers. Among the studies included, one study observed a 96% reduction of COVID-19 risk among Chinese healthcare workers using facemasks [64]. A recent study also demonstrated face coverings as effective preventive measures in slowing down the viral transmission via droplets by mimicking cough-generated airborne particles in an indoor environment. The study showed that surgical and K95/KN95 masks reduced cough droplets dramatically [65]. By utilizing COVID-19 cases from 190 countries between January 23rd, 2020, and April 13th, 2020, non-pharmacologic prevention initiatives (NPIs), such as mandatory masks, quarantine, distancing and traffic restriction, were inversely associated with the reproduction number of COVID-19. The reductions in reproduction numbers were −15.14% (from −21.79% to −7.93%) for mandatory facemask and −42.94% (from −44.24% to −41.60%) for distancing. When two or more interventions were implemented simultaneously, a greater decrease in the reproduction number of COVID-19 was observed [66]. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified as the definitive infectious agent; however, social

and environmental factors, such as air pollution, may also play a contributory role in the transmission of the virus in human population [67].

$PM_{2.5}$ may affect disease via a variety of mechanisms such as altering immune response, increasing oxidative stress, causing inflammatory injury, inducing mutagenicity and introducing respiratory tract damage [51-53]. Moreover, ambient air pollution was associated with various infectious outcomes, such as deaths due to lower respiratory infection [56], elevated fatality of severe acute respiratory syndrome (SARS) in China [68], increased risk of influenza [69], and upper respiratory infections incidence and hospital admission for respiratory infections [70]. In addition, SARS-CoV-2 can remain viable in aerosols for hours [71] and air particles are suspected to be capable of carrying the virus and facilitating its spread [72].

Table 2-1 summarizes current literature on the association between air pollution and COVID-19 outcomes. Studies in Northern Italy and among cities in China reported positive correlations between short-term exposure to $PM_{2.5}$ and COVID-19 outcomes [73-77]. A Korean study concluded temporal association between COVID-19 incidence and other air pollutants, but not with $PM_{2.5}$ [78]. Exposure to long-term $PM_{2.5}$ was associated with COVID-19 mortality after controlling for different confounders [79-84]. In the United States, Wu et al. showed that each 1-$\mu g/m^3$ increase in long-term $PM_{2.5}$ exposure (2000–2016 annual average) was associated with 11% increase in COVID-19 mortality [79], which was also affected by the presence of other hazardous air pollutants [80]. Hendryx et al. showed a positive association between long-term $PM_{2.5}$ and COVID-19 prevalence and fatality as of May 31st, 2020, by applying a linear regression model [84]. Timely evidence on the association between long-term exposure to air pollution, especially $PM_{2.5}$, and COVID-19 incidence is accumulating in the US and in Europe based on arbitrary cut-off points of the pandemic. With the progression of COVID-19, more

extensive data would allow us to examine whether COVID-19 incidence was associated with long-term exposure to $PM_{2.5}$ during each surge of the pandemic and whether it might be modified by the implementation of NPIs, such as facemask mandates or stay home policies.

2.2 Methods

Data sources are summarized in Table 2-2. Specifically, county-level COVID-19 incidence data was obtained from Johns Hopkins University, Center for Systems Science and Engineering Coronavirus Resource Center (CSSE). County-level confirmed numbers of cases of 3,261 counties across the US have been updated daily utilizing the data from the CDC and state departments of health since January 21st, 2020 [13]. The fewest 7-day average daily confirmed cases (20,764 cases on May 28th and 34,596 cases on September 12th, 2020) corresponded to the lowest point after each of the first two surges and thus marked the end of that surge. In this study, we used the cumulative incidence cases of COVID-19 reported in each county up to May 28th, 2020, and up to September 12th, 2020.

County-level annual average of $PM_{2.5}$ between 2000 and 2016 as well as county-level covariates were available on a GitHub repository. The data utilized in the study assessing COVID-19 mortality and long-term exposure to $PM_{2.5}$ was published by Wu et al. on this repository and was publicly available [79]. Briefly, van Donkelaar et al. estimated the ground-level concentration of $PM_{2.5}$ using a chemical transport model and satellite observation calibrated using ground-level observation across North America [85].

County-level socioeconomic and demographic variables in 2016 were available from the US Census/American Community Survey. The 2020 behavioral factors such as prevalence of adult

tobacco smoking and adult obesity were publicly accessible on the County Health Rankings & Roadmaps program, a program of the University of Wisconsin Population Health Institute aiming to provide a reliable and sustainable source of local data [86]. State average was used to replace missing values at county-level prevalence for smoking and obesity. State-wide policy of facemask mandates and stay home orders were collected and maintained by Boston University School of Public Health [63]. The New York Times summarized reopening policy for each state [87]. Up to date data on total tests performed in each state are available on the COVID tracking project [88]. A total of 165 counties were excluded because of the lack of a valid Federal Information Processing Standard code (n = 10) or missing covariates (n = 155). After exclusion, a total of 3,096 counties were eligible and included in the study.

This study aimed to estimate how COVID-19 incidence was associated with county-level long-term exposure to ambient $PM_{2.5}$ and with state policies of facemask mandates and stay home orders during the first surge (as of May 28th, 2020), during the second surge (between May 29th, 2020, and September 12th, 2020) and cumulatively (as of September 12th, 2020). Since the COVID-19 temporal relationship with long-term exposure to $PM_{2.5}$ is different from that with preventive interventions, separate negative binomial models were applied. Models were adjusted for potential confounders (Equation 1 and 2).

$$\begin{aligned}\log[E(\text{Incidence}_i)] &= \beta_0 + \beta_1 PM_{2.5} + \beta_2 \text{ populatoin density} + \beta_3 \text{ percentage of poverty} \\ &+ \beta_4 \text{ median house value} + \beta_5 \text{ meidan household income} \\ &+ \beta_6 \text{ percentage of owner occupied property} + \beta_7 \text{ percentage of African American} \\ &+ \beta_8 \text{ percentage of Hispanic} + \beta_9 \text{ percentage of population less than high school education} \\ &+ \beta_{10} \text{ smoke rate} + \beta_{11} \text{ obese rate} + \beta_{12} \text{ percentage of male} \\ &+ \beta_{13} \text{ percentage of people with age of 65 and above} \\ &+ \beta_{14} \text{duration since first case reported} + \beta_{15} \text{reopening} + \beta_{16} \text{pausing reopened} \\ &+ \beta_{17} \text{ total tests performed} + \beta_{18} \text{ facemask mandate} + \beta_{19} \text{ days of stay home order} \\ &+ \text{offset[log(population)]}\end{aligned} \quad (1)$$

$$\log[E(\text{Incidence}_i)] = \beta_0 + \beta_1 PM_{2.5} + \beta_2 \text{ populatoin density} + \beta_3 \text{ percentage of poverty} + \beta_4 \text{ median house value} + \beta_5 \text{ meidan household income} + \beta_6 \text{ percentage of owner occupied property} + \beta_7 \text{ percentage of African American} + \beta_8 \text{ percentage of Hispanic} + \beta_9 \text{ percentage of population less than high school education} + \beta_{10} \text{ smoke rate} + \beta_{11} \text{ obese rate} + \beta_{12} \text{ percentage of male} + \beta_{13} \text{ percentage of people with age of 65 and above} + \beta_{14}\text{duration since first case reported} + \beta_{15}\text{reopening} + \beta_{16}\text{pausing reopened} + \beta_{17} \text{ total tests performed} + \beta_{18} \text{ facemask mandate} + \beta_{19} \text{ stay home order} + \beta_{20}\text{incidence 14 days prior} + \text{offset}[\log(\text{population})] \quad (2)$$

County-level annual average of ambient $PM_{2.5}$ between 2000 and 2016 was used as a measure for long-term exposure to $PM_{2.5}$. Equation 1 was used to investigate the association between exposure to long-term $PM_{2.5}$ and COVID-19. We adjusted for duration since the first case reported, population density, poverty, education, proportions of African Americans and Hispanic Americans, owner occupied property, median house value, median household income, gender, population older than 65 years old, and prevalence of tobacco smoking and obesity at county level and state-level variables, including policies of facemask mandates and the duration of stay home orders, total test results reported and reopening status. To examine the association between intervention policies and COVID-19 incidence as in equation 2, facemask mandates and stay home orders were measured as binary variables. Their values as of May 28th, 2020, were used to examine the association during the first surge and the values as of September 12th, 2020, were used for the second surge and for both surges cumulatively. This also applied to other variables that changed over time, including duration since the first case reported, duration of stay home orders, total tests reported and reopening status. To address the potential reserve causation that policies might be a result of elevated COVID-19 incidence, we additionally controlled for COVID-19 incidence 14-days prior (as of May 14th, 2020, for the first surge and as of August 28th, 2020, for the second surge and for the cumulative analysis). To account for the correlation

within each state, we applied the robust error estimation [89]. Stratified analyses by facemask mandates and stay home orders were performed by applying equation 1 to evaluate their effect measure modification on the association between $PM_{2.5}$ and COVID-19 incidence. Relative risk (RR) and 95% confidence interval (CI) were reported. Analyses were performed in SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

2.3 Results

A total of 3,096 counties across the United States are included in this study and their characteristics are presented in Table 2-3. As of September 12th, 2020, the average COVID-19 incidence was 1.65%, with a median of 1.29%. Counties with COVID-19 incidence greater than the national median had higher average annual $PM_{2.5}$ concentration, earlier occurrence of the first case, more tests performed, and were less likely to be reopened. Higher population density, higher proportion of African Americans and Hispanic, population in poverty, population with less than a high school education and less owner-occupied properties were also observed in counties with increased incidence of COVID-19.

Table 2-4 shows the association found between ambient $PM_{2.5}$ and COVID-19 infection after adjusting for potential covariates. Overall, each 1-$\mu g/m^3$ increase in annual average concentration of $PM_{2.5}$ was associated with increase in the cumulative COVID-19 risk, with a RR of 1.0756 (95% CI: 1.0376. 1.1149). This association was consistent over two surges of the pandemic, with a RR from 1.0506 (95% CI: 0.9857, 1.1197) to 1.0852 (95% CI: 1.0361, 1.1366) for each 1-$\mu g/m^3$ increase in $PM_{2.5}$.

In counties eligible for this study, 1,853 were located in states that had ever issued a facemask or face covering mandate. The RR of COVID-19 incidence for a county located within a state requiring facemask was 0.8466 (95% CI: 0.7598, 0.9432) as of September 12th, 2020, after controlling for incidence case number 14 days prior (August 28th, 2020) and other covariates (Table 2-4). A similar association was observed during the second surge (between May 29th and September 12th, 2020), with RR of 0.8360 (95% CI: 0.7298, 0.9577). However, facemask mandates seemed to have little impact on the incidence during the first surge (as of May 28th, 2020), with the RR of 0.9889 (95% CI: 0.8667, 1.1283).

State-wide stay home policy (ever) was issued in 2,659 counties. After adjusting for incidence of August 28th and other covariates, we observed reduction in COVID-19 incidence among the counties with effective stay home policy, with a RR of 0.9193 (95% CI: 0.8021, 1.0537) (Table 2-4). Stay home policy showed similar protective effect during the second surge (RR = 0.9168, 95% CI: 0.7833, 1.0730) and this effect was stronger during the first surge (RR = 0.7615, 95% CI: 0.5619, 1.0321).

Since facemask mandates and stay home policy might be potential effect modifiers on the association between $PM_{2.5}$ and COVID-19, we performed stratified analyses by facemask policy (ever issued/never issued) and by stay home policy (ever issued/never issued). Results are shown in Table 2-5. Though the incidence associated with 1-$\mu g/m^3$ increase in $PM_{2.5}$ seemed to be similar overall and during the first surge, this association was enhanced among counties locating in state with a facemask policy (RR = 1.1161, 95% CI: 1.0640, 1.1708) compared to those not requiring a facemask (RR = 1.0417, 95% CI: 0.9905, 1.0955). Those counties locating in a state without an effective stay home order experienced higher COVID-19 risk associated with 1-$\mu g/m^3$ increase in $PM_{2.5}$ (RR = 1.4050, 95% CI: 1.2961, 1.5230 for the first surge; RR = 1.1543,

95% CI: 1.1016, 1.2095 for overall), whereas slight increase was still observed overall (RR = 1.0798, 95% CI: 1.0386, 1.1226) and during the first surge (RR = 1.0186, 95% CI: 0.9565, 1.0848) in counties with an effective stay home order.

2.4 Discussion

Our study utilizing data up to September 12th, 2020, from 3,096 counties across the United States suggested that each 1-μg/m^3 increase in long-term $PM_{2.5}$ was associated with a 7.56% increase in COVID-19 incidence. Our data also suggested that preventive interventions, including facemask mandates and stay home orders, reduced the risk of COVID-19 by 15% and 8%, respectively. However, implementation of facemask mandates or stay home orders did not modify the association between long-term exposure to $PM_{2.5}$ and COVID-19 incidence. The potential mechanisms for the impact of $PM_{2.5}$ include (1) long-term exposure to $PM_{2.5}$ might lead to chronic inflammation in the respiratory pathway, which predisposes individuals to COVID-19; (2) chronic exposure to $PM_{2.5}$ might impair cilia, which acts as the first line of defense; as a result, people with abnormal cilia might be more vulnerable to any viral infection [85]; and (3) finally, $PM_{2.5}$ exposure induces the over-expression of angiotensin-converting enzyme 2 (ACE2), which is the receptor SARS-CoV-2 binds to; this might also lead to increasing susceptibility to be infected [7, 90].

These findings built on earlier findings by showing that long-term exposure to $PM_{2.5}$ is a risk factor and by showing that the levels of exposure to $PM_{2.5}$ in the US are sufficiently high to increase the risk of COVID-19. Our results were consistent with the association between long-term exposure to $PM_{2.5}$ and COVID-19 mortality. Wu et al. reported that each 1-μg/m^3 increase

in long-term $PM_{2.5}$ was associated with 11% increase in COVID-19 mortality using the same exposure window and geographic location [79]. Our finding that long-term exposure to $PM_{2.5}$ increased the risk of COVID-19 using the negative binomial models was consistent with the positive correlations reported by studies in Europe and in the US, employing different statistical models (Table 2-1) [81-84]. Thus, we provided an alternative perspective to examine such association when the linear assumption between COVID-19 incidence and $PM_{2.5}$ concentration might not hold.

Previously, a study in the US, using county-level data as of May 31st, 2020, applied a linear regression model and suggested that an additional 23.5 COVID-19 cases were associated with each 1-$\mu g/m^3$ increase in 2016 annual average $PM_{2.5}$ concentration [84]. We confirmed the positive correlation and updated the COVID-19 incidence cases as of September 12th, 2020. Other than using an arbitrary cut-off point, we examined the trend of the pandemic and selected the date corresponding to the end of each surge. Moreover, we applied a longer exposure window from 2000 to 2016 to better represent the long-term $PM_{2.5}$ exposure than using a single-year average concentration. Potential bias due to disease progression was addressed by including additional confounders, such as days since the first case reported. In addition, we also consider the potential effect modification by facemask mandates or stay home orders.

This is the first study to examine how the association between long-term $PM_{2.5}$ exposure and COVID-19 incidence may be affected by state prevention policies, including facemask mandates and stay home policy. Importantly this study suggests a mitigation effect of stay home and face mask policies. Facemask mandates showed stronger protective effect toward later course of the pandemic (Table 2-4). This might be because the consciousness of wearing face coverings in public and the supply of face coverings increased as the pandemic progressed. Wearing

facemasks is an effective way of preventing viral transmission via coughing droplets [65] and reduces infection of COVID-19 among health care workers [64]. Moreover, stay home order seemed to be more effective at the beginning of the pandemic (Table 2-4) and, as the virus spread slowed down, states tended to terminate such orders. This diluted the associations we observed for the later stage of the pandemic. Stay home orders, also known as lockdown, was associated with reduced air pollution in many countries [72, 91-96], including the US [93]. During lockdown, reduced overall mortality was observed in China [94]; less excess life cancer risk was estimated in India [95]; and saving due to reduced morbidity might meanwhile relieve economic loss [97]. Therefore, stay home orders might help to alleviate the burden of COVID-19 incidence via the reduction of virus transmission among individuals as well as reduced exposure to air pollution, which is a risk factor for COVID-19.

The study was subject to several limitations. First, due to the nature of the ecologic study design, the results might be vulnerable to ecologic fallacy. In addition, we might still have residual confounding even after controlling for county-level and state-level covariates. Moreover, our exposure data for $PM_{2.5}$ ends in 2016, which was 4 years before the pandemic. However, the previous exposure may still serve as an indicator for more recent ambient exposure and our result was consistent with the positive findings between short-term $PM_{2.5}$ exposure and COVID-19 incidence previously reported [73-76]. Implementation of and compliance with facemask mandates and stay home policies might cause misclassification. However, this would dilute the effect and lead to more conservative estimates on the preventive effects. Though the incidence 14 days prior was controlled when assessing the association of policies, reverse causation might still be an issue, moving estimates towards the null.

Further research should examine whether some of the elevated risk experienced by communities of color and low-income communities in the US is due to higher exposure to air pollution. Potential policy implications of these findings include (1) the importance of further lowering the long-term exposure to $PM_{2.5}$ in the US and (2) the heightened importance of stay home and face mask policies among populations with air population exposure.

Our study added evidence that long-term $PM_{2.5}$ exposure increased reported COVID-19 cases in the community during each of the first two surges and cumulatively as of September 12th, 2020, in the US. Although both state-level implementation of facemasks mandates and stay home orders were effective in preventing the spread of COVID-19, no clear effect modification was observed with long-term exposure to $PM_{2.5}$ on the risk of COVID-19.

CHAPTER 3. IMPACT OF SARS-COV-2 VACCINES ON COVID-19 INCIDENCE AND MORTALITY IN THE UNITED STATES

3.1 Introduction

Since being recognized in December, 2019, the Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2) pandemic has caused more than 479 million cases and six million deaths worldwide [98]. The United States has been particularly affected, with almost 80 million Coronavirus 2019 (COVID-19) infections and 972 thousand deaths reported as of March 25th, 2022 [13]. Though a number of non-pharmacologic prevention initiatives (NPIs) have been introduced to slow SARS-CoV-2 transmission [1], vaccines are now recognized as among the most effective means for preventing COVID-19 cases and deaths [99].

Three vaccine preparations are authorized for use in the US. The BNT162b2 vaccine (Pfizer, Inc. and BioNTech) and the mRNA-1273 (Moderna) vaccine have full US Food and Drug Administration (FDA) approval [100, 101], while JNJ-78436735 (Janssen Pharmaceuticals) is available under an emergency use authorization. All three vaccines are effective in preventing SARS-CoV-2 infections and COVID-19 associated diseases, hospitalizations, and deaths [102-104], though vaccine effectiveness wanes over time and breakthrough infections occur [99, 105].

Numerous studies have demonstrated that SARS-CoV-2 vaccines are effective in preventing COVID-19 infections and disease in individuals outside of clinical trials, including among health care workers, first responders, individuals attending ambulatory clinics, veterans, and in nursing homes [106-108]. However, vaccine waning has been reported, especially after 6 months being fully vaccinated [109-111]. Vaccine effectiveness also varies by SARS-CoV-2 variant. Omicron, the most recent predominant variant, evades infection- or vaccination-induced immunity more

effectively than Delta variant, and correspondingly has higher rates of breakthrough infections or disease reported compared with other variants [109, 111-113]. With the previous recognition of waning vaccine immunity and the rise of Delta as the predominant SARS-CoV-2 variant in the US, the FDA authorized the emergency use of one or two boosters for COVID-19 vaccines, including the use of a heterologous booster [114-116]. Studies showed the effectiveness of vaccines improved after a booster dose, including against Omicron [111, 117, 118].

Despite the proven safety and effectiveness of these vaccines, a substantial minority of the adult US population remains resistant to getting vaccinated [119]. To understand the impact of SARS-CoV-2 vaccines, it is imperative to evaluate the impact of vaccination on community-wide SARS-CoV-2 cases and COVID-19 disease, not just among those vaccinated—a concept popularly referred to as "herd immunity" [120]. Moreover, it is worth examining whether and by how much such an impact might differ corresponding to different dominant strains in the community. To investigate the impact of population percentages of SARS-CoV-2 complete vaccination on community-wide COVID-19 case and mortality rates, we undertook an ecological analysis of US county vaccination rates on reported county COVID-19 cases and deaths, controlling for socioeconomic, demographic, comorbid conditions, rural/urban, air pollution, and related factors, the introduction of NPIs and the presence of most prevalent strain in the US

3.2 Methods

Poisson distribution with generalized linear models [121] were used to estimate associations between cumulative US county-level complete vaccination rates of all age groups and the daily change in county-wide COVID-19 incidence and mortality between April 23rd, 2021, and March

25th, 2022. The dates represent when Delta was first recognized in the US to the end of the study period. The analyses were divided into three periods to account for the most dominant strain in the US during each period. The first period was from April 23rd to July 2nd, 2021 before the Delta predominance and when Alpha was the most prevalent strain. Delta was responsible for the majority of reported US COVID-19 cases from July 3rd to December 1st, 2021. Between December 2nd, 2021 and March 25th, 2022, Omicron began circulating in the US and replaced Delta to become the dominant strain.

All models were adjusted for the following potential confounders: annual average $PM_{2.5}$ between 2000 and 2018, population density, poverty, education, proportions of White, proportions of male, proportion of population older than 65 years old, owner-occupied property, median house value, median household income, percentage of people without health insurance, proportion of people living in rural area, prevalence of tobacco smoking, and obesity. All covariates were measured at the county level. State-level variables for NPIs policies (facemask mandates, stay home orders) also were included in models. Table 3-1 summarizes the data source.

County-level COVID-19 incidence and mortality data were obtained from the Johns Hopkins University, Center for Systems Science and Engineering Coronavirus Resource Center (CSSE). CSSE collects county-level confirmed numbers of cases and deaths of 3,342 counties across the US from the US Centers for Disease Control and Prevention (CDC) as well as state departments of health since January 21st, 2020 [13].

County-level vaccine data were obtained from Covid Act Now. These data are derived from the US Department of Health and Human Services, the CDC, the New York Times, and official state and county dashboards. Data on vaccinations initiated, vaccination regimens completed and booster shots received were available for all 50 states [122]. To allow for the development of

protective immunity after vaccination, a two-week lag was introduced after people were completely vaccinated (a person vaccinated on June 18th was considered fully protected by July 2nd). The two-week lag also was used to account for time between exposure and development of COVID-19 disease. To assess the impact of vaccination on COVID-19 mortality, a four-week lag was used (vaccinated by September 2nd to assess the impact on mortality on September 30th). County-level annual average of $PM_{2.5}$ between the years 2000 and 2018, as well as county-level covariates, were available from the Atmospheric Composition Analysis Group [85]. County-level socioeconomic and demographic variables for 2020 were available from the US Census/American Community Survey. 2020 data on the prevalence of adult tobacco smoking and adult obesity and the proportion of people living in rural area were accessible through the County Health Rankings & Roadmaps program [86]. State averages were used to replace missing values for county-level prevalence for smoking and obesity. State-wide non-pharmacologic prevention policies, including facemask use and stay home orders, were obtained from the Boston University School of Public Health [63].

Counties with invalid Federal Information Processing Standards (n = 10), missing covariates (n = 98), missing vaccination status with a 2-week (n = 113) or a 4-week (n = 122) lag, and negative change in incidence (n = 48) or in mortality (n = 70) possibly due to data entry error were excluded. As a result, data from 3,073 counties in 48 states were available to investigate the association between population vaccination rates and county-wide COVID-19 incidence and 3,042 counties in 48 states to investigate the association between vaccination rates and COVID-19 mortality. Among these eligible counties, 2,906 counties in 46 states and 2,876 counties in 46 states also reported percentage of people receiving a booster shot during the Omicron predominance and were utilized to assess the association between booster coverage and COVID-

19 incidence and mortality, respectively (Table 3-3). Relative risks (RR) and 95% confidence intervals (CI) are reported. Analyses were performed in SAS 9.4 (Cary, NC).

3.3 Results

Among the 3,073 counties across 48 states, the average county total population complete vaccination rate was 50.79% as of March 11th, 2022. Counties with complete vaccination rates above the national median (49.8%) had higher median house values, higher median household incomes, higher population density, and less population living in rural area compared with counties with vaccination rates below 49.8%. These counties also were more likely to be located in states where a facemask policy or a stay-home order was ever issued before July 2nd, 2021 (Table 3-2).

When Alpha was the dominant strain in the US, each percentage increase in a county's total population complete vaccination rate was associated with a 4% decrease in county-wide COVID-19 cases (RR = 0.9607, 95% CI: 0.9553, 0.9661) and with a 3% reduction in COVID-19 mortality (RR = 0.9694, 95% CI: 0.9653, 0.9736). However, county-level complete vaccine coverage was not associated with decreases in COVID-19 cases during the Delta (RR = 0.9988, 95% CI: 0.9964, 1.0011) and Omicron (RR = 0.9969, 95% CI: 0.9919, 1.0019) predominance. The association between complete vaccination rates and COVID-19 mortality declined to less than 0.1% (RR = 0.9934, 95% CI: 0.9889, 0.9980) when Delta accounted for the majority of reported cases in the US between July 3rd and December 1st, 2021. When Omicron began circulating, complete vaccination rate was associated with a slight increase of 0.6% in county-level COVID-19 mortality (RR = 1.0061, 95% CI: 1.0022, 1.0101). In contrast to the associations between complete vaccination rates and COVID-19 outcomes during the Omicron

predominance, a 6% reduction in COVID-19 incidence (RR = 0.9356, 95% CI: 0.9235, 0.9479) and a 4% reduction in COVID-19 mortality (RR = 0.9595, 95% CI: 0.9431, 0.9761) were observed with each percentage increase in people receiving a booster shot at the county level (Table 3-3).

3.3 Discussion

Data from 3,073 counties across 48 states demonstrates that the associations between county-level complete vaccination rate and COVID-19 incidence and mortality varied based on the most prevalent SARS-CoV-2 variant circulating in the US between April 23rd, 2021 and March 25th, 2022 after adjusting for potential confounders. The protective associations between county-level complete vaccination rate and COVID-19 incidence and mortality were observed during the Alpha predominance, but such associations attenuated later when Delta or Omicron was the most prevalent strain in the US. However, after booster shots were available, the increase in the county percentage of people receiving a booster shot was associated with reduction in both COVID-19 incidence and mortality between December 2nd, 2021 and March 25th, 2022.

This study is among the first to show the population-wide association between SARS-CoV-2 vaccination rate and COVID-19 incidence and mortality stratified by the predominant strain circulating in the country. The results show that county-level vaccination rate has different associations with COVID-19 incidence and mortality during different periods in the US. The protection was highest shortly after COVID-19 vaccines became widely available while Alpha was the predominant circulating strain and declined in later periods. This pattern might be due to the waning effect of the vaccines against infection over time within the community. A meta-

analysis showed that though vaccine effectiveness against SARS-CoV-2 infections was reduced, vaccine remained highly efficient in protecting people from severe diseases due to COVID-19 [110]. In addition, as vaccine uptake increased and cases declined, most states lifted their NPIs orders [63]. Without the protection of NPIs and given the waning of vaccine effectiveness, people became more susceptible to COVID-19 infection even when fully vaccinated. Besides the waning vaccine effectiveness, our results also suggest the association of vaccine coverage and COVID-19 incidence might depend on the most prevalent strain in the community. The protection of increased vaccination coverage against county-level COVID-19 incidence was not observed when Omicron circulation predominated, which has been shown to evade previous immunity more than Alpha or Delta [112]. In the light of the waning vaccine effectiveness and breakthrough cases, a booster shot has been recommended. Individual-level and experimental data demonstrate that a third dose of mRNA COVID-19 vaccines increases vaccine efficacy [111, 112]. Similarly, our results also suggest that the increasing uptake of a booster shot is associated with the reduction in community COVID-19 cases and deaths, indicating possible spillover protective effects as the percentage reductions in population COVID-19 cases and deaths generally exceeded the percentage increases in population proportion of people receiving a booster shot.

The study was subject to several limitations. First, ecologic study designs are vulnerable to the ecologic fallacy. Therefore, caution is required when interpreting the study results, especially when extrapolating population findings to the individual level. In addition, we cannot rule out the possibility of residual confounding even after controlling for numerous county-level and state-level covariates. Using COVID-19 reported cases may underestimate of the number of actual infections due to under-testing of asymptomatic patients, especially when self-tests became

widely available. However, alternative estimates for cumulative incidence, such as seroprevalence [123], also have limitations including sampling bias, test sensitivity and specificity, and the progress of the pandemic [124]. Our analysis was not able to assess the impact of the three different vaccines currently available in the US, which likely had different efficacies. Although a detailed distribution of different variants in the US was not available, we examined the associations stratified by the most dominant strain. Therefore, our results represent the associations between vaccine rates overall and COVID-19 incidence and mortality in the US for vaccines as actually deployed and SARS-CoV-2 variants as they circulated during the period of our analysis.

Nevertheless, this study is the first to estimate the association between complete vaccination rates and COVID-19 incidence and mortality in the US general population using county-level data. This nation-wide study covers 3,073 counties in 48 states across the entire country, showing the population-based impact of increasing complete vaccination rates, as well as increasing percentage of those receiving a booster shot. Our results agree with the observation of waning effectiveness over time and higher infection breakthrough rates due to the Omicron variant. However, increasing the coverage of booster shot appear to be an effective way to protect individuals in the community and to potentially to achieve herd immunity.

CHAPTER 4. AIR POLLUTION AND LUNG AND UADT CANCERS SUSCEPTIBILITY IN LOS ANGELES

4.1 Introduction

Air pollution and particulate matters (PM) in ambient air pollution are known carcinogen to humans and are regarded as the most widespread environmental carcinogen [55]. Household air pollution (HAP) from solid fuels remained among the leading global risk factors for deaths and disability-adjusted life-years, accounting for 2.8 million deaths in 2015 [56].

Studies have investigated the association between exposure to ambient air pollution and either incidence or mortality of lung cancer around the world, though there are still inconsistent findings [125-135]. These studies reported lung cancer incidence and mortality either separately, considering two as separate events of interest, or together, treating mortality as an indicator for incidence based on the high fatality of lung cancer [60, 136-141]. In the US, 5 perspective cohorts among general population [142-150] and two cohorts linking different registries [151-153] investigated the association between air pollution and lung cancer incidence or mortality. Only one study examined how air pollution might affect lung cancer survival [154]. Meta-analyses suggest about 10% increase in lung cancer risk associated with 10-$\mu g/m^3$ increase in $PM_{2.5}$ [137-139]. Such association appeared to be stronger among never or former smokers [141, 147, 149].

Though a study demonstrated a large increase in lung cancer susceptibility when accounting for various sources of HAP [155], many studies invested the association between lung cancer and HAP due to specific emission sources, such as biomass fuel burning and environmental tobacco smoking (ETS). Solid fuel use is associated with lung cancer in many developing countries [156-

159]. In addition, females may be more vulnerable to develop lung cancer being exposed to solid fuels [160]. Environmental tobacco smoking (ETS) is another major source of HAP that is associated with increased risk of lung cancer [160-163].

Unlike the association between air pollution and lung cancer, few studies have investigated the association between air pollution and UADT cancers. A European study concluded a marginally positive association (HR = 1.05 per 5.0-$\mu g/m^3$, 95% CI: 0.62, 1.77) between $PM_{2.5}$ and UADT cancer risks [164]. Furthermore, studies in Asia found that increased $PM_{2.5}$ was associated with specific sites of UADT cancers, such as nasopharynx [165], oral cavity [166], and esophagus [134]. However, a US study showed null associations between $PM_{2.5}$ and site-specific UADT cancers mortality, probably due to the lack of power [167].

Though the majority of studies were conducted in developing countries, studies suggested that the use of solid fuels is associated with increased risks of site-specific UADT cancers [168-174]. Positive associations between ETS exposure and specific site of head and neck cancer (HNC) were suggested [175-178]. In addition, a dose-response pattern was reported between ETS exposure and HNC [177, 179]. However, power is an issue to studies not only investigating the association between ETS and HNC [161, 180], but also the ones examining how ETS is associated with esophageal cancer [181, 182].

Though studies tried to investigate that association between air pollution and lung cancer risk or mortality, the results are somewhat inconsistent among studies, not to mention the magnitude, suggested by the large I^2 value of 53.0% for $PM_{2.5}$ [60]. Moreover, most of these studies covered population across different geographic regions and over long period of time, which the source of emission might vary a lot. Especially, the composition of PM, which has different health effects,

could change. Hence, due to the heterogeneity of the association, it might not be appropriate to simply transpose findings to other populations. Limited evidence was available on the association between ambient air pollution and UADT cancers and most of these studies were under power. To our knowledge, this is the first study to examine the association between ambient $PM_{2.5}$ and lung and UADT cancers susceptibility utilizing population-based data in Los Angeles (LA) with the availability of individual-level confounders and addressing the indoor air pollution at the same time.

4.2 Methods

The LA study, a population-based case-control study conducted in the LA county from 1999 to 2004, was analyzed to investigate the association between air pollution and lung and UADT cancers. The study was approved by the Institutional Review Boards of University of California at Los Angeles (UCLA) and University of Southern California (USC). Informed consent was obtained from each participant. To meet the eligibility criteria for the LA study, all subjects were (a) residents of LA County at the time of diagnosis for cases or at the time of recruitment for controls; (b) between 18 and 65 years old during the study period, 1999 to 2004; and (c) English or Spanish speakers, or with translators at home.

The USC rapid ascertainment system of the Cancer Surveillance Program for LA County is a population-based cancer registry for the LA County, collecting basic clinic and demographic information on all invasive cancer in the area, and was used to identify incident cases of lung and UADT cancers during the study period. Among cases, over 95% were histologically verified and the rest were confirmed by other diagnostic methods, such as magnetic resonance imaging and

computed tomography scan. Participation rates and the reasons for nonparticipation among eligible cases varied across different subsites. The participation rate for lung cancer was 39% and the lowest participation rate among UADT cancers was esophageal cancer at 35%, followed by laryngeal cancer (42%), pharyngeal cancer (45%), and oral cancer (54%). The nonparticipating reasons for lung cases were death (25%), refusal (16%), inability to establish contact (14%), ill health (5%), and refused permission by the case's physician (1%) and the one for UADT cases were refusal (21%), inability to establish contact (18%), death (10%), and ill health (4%). Though there was no obvious difference in age and gender between enrolled cases and nonparticipating cases, African Americans had a lower participation rate comparing to other racial/ethnic groups. The LA study enrolled 611 incident lung cancer cases (ICD-O2 C33.9-34.9), including 297 (49%) adenocarcinomas, 115 (19%) large cell carcinomas, 95 (15%) squamous cell carcinoma, 75 (12%) small cell carcinomas, and 29 (5%) lung cancers with other histologic types. Among 601 eligible participants diagnosed with UADT cases, there were 303 oral cancers (C01.9-C09.9), 100 pharyngeal cancers (C10.0-C14.0, C30.0-C31.1), 90 laryngeal cancers (C32.0-C32.9), and 108 esophageal cancers (C15.1-C16.0). All 76 adenocarcinomas of UADT occurred at the site of esophagus, accounting for 69% of all esophageal cancers. Other histologic types of esophageal cancers were 32 (30%) squamous cell carcinomas and 2 (2%) cases with other histological types. The majority (465 cases or 94%) of other UADT cancers were squamous cell carcinomas and small portion (28 cases or 5%) were non-esophagus UADT cancers with other histological types [183].

Eligible controls were selected from the general population and individually matched to cases on age decade, gender, and residential neighborhood. Individuals with previous diagnoses of lung and UADT cancers, indicated by Cancer Surveillance Program records and verified during

interview were excluded from control group. Controls were selected from a sequence of 30 to 40 households in the same neighborhoods as cases based on a predefined algorithm. However, the household sequence was expanded if no eligible or willing controls were identified. The participation rates among controls were 72% and refusal (19%) and inability to establish contact (8%) were reasons for nonparticipation. Females were more likely to respond among controls [183]. A total of 1040 controls, including 562 controls matched to lung cancer cases and 478 controls matched to UADT cases, participated in the study.

In this study, based on the detailed information collected for tobacco use and alcohol drinking, smokers were defined as those smoking a total of at least 100 cigarettes in their lifetime and alcohol drinkers were those ever consumed at least one alcoholic drink (including beer, wine, or liquor equivalent to 14 grams of alcohol) per month for a period of at least six months. Pack-years, one of which is equivalent to smoking 1 pack of cigarettes per day for 1 year, and drink-years, one of which indicates consuming 1 alcoholic drink of any kind per day for 1 year, were used as cumulative measures of tobacco smoking and alcohol drinking.

Address at diagnosis for cases and at reference date for controls were geocoded to latitude and longitude coordinates using address locators. Annual average concentration of ambient $PM_{2.5}$ concentrations from 1998 to 2018 at each geocoded address were obtained from the Atmospheric Composition Analysis Group [85]. $PM_{2.5}$ concentration 1-year before the diagnosis or reference date was assessed.

Solid fuel used for cooking or heating included use of fireplace, wood, coal, oil and kerosene, since adulthood and exposure to ETS since adulthood were obtained from the questionnaire.

Exposure to HAP would be defined as being exposed to any of these two sources since adulthood.

Air pollution index (API) was computed based on exposure to any HAP since adulthood, including exposing to above-mentioned solid fuels for cooking or heating or exposing to ETS at home, and exposure to ambient $PM_{2.5}$ based on the tertile score (0 for tertile 1, 1 for tertile 2, and 2 for tertile 3).

Among 611 lung cancer cases, we excluded those who cannot be geocoded (n = 6), with missing $PM_{2.5}$ (n = 21), missing covariates (n = 2), and missing ETS (n = 2) and HAP (n = 3) since adulthood. Among 601 UADT cancers cases, we excluded those who cannot be geocoded (n = 3), with missing $PM_{2.5}$ (n = 26), missing covariates (n = 3), and missing ETS (n = 3) and HAP (n = 1) since adulthood. Among 562 controls matched to lung cancer cases, we excluded those who cannot be geocoded (n = 1), with missing $PM_{2.5}$ (n = 24), and missing covariates (n = 1), missing ETS (n = 1) since adulthood. Among 478 controls matched to UADT cancers cases, we excluded those with missing $PM_{2.5}$ (n = 26), and missing covariates (n = 1), and missing ETS (n = 3) since adulthood. As a result, the final analytical set included 577 lung cancer cases, 565 UADT cancer cases, 535 lung cancer controls, and 448 UADT cancers controls.

To account for the potential overmatching or selection bias due to matching on residential neighborhood, we used two sets of control, the combined control and the swapped control (i.e., using UADT controls for lung cancer analysis and lung cancer controls for UADT analysis), to assess the association between air pollution and lung and UADT cancer susceptibility. Unconditional logistic models were used to assess the association between lung and UADT cancers and ambient $PM_{2.5}$, exposure to ETS or HAP since adulthood, and air pollution index

(API). Ambient $PM_{2.5}$ was measured as continuous (per 1-$\mu g/m^3$) and using median (below median: $\leq$ 19.1 $\mu g/m^3$ vs. above median: > 19.1 $\mu g/m^3$) and tertiles (Tertile 1: $\leq$ 17.9 $\mu g/m^3$; Tertile 2: 17.9 $\mu g/m^3 < PM_{2.5} \leq 20.9$; and Tertile 3: > 20.9 $\mu g/m^3$) of the combined controls.

Unconditional logistic regression models were adjusted for potential confounders, including age, gender, education (less than high school, high school, some college, college, or graduate school), race/ethnicity (non-Hispanic White, African American, Hispanic, or Other), smoking (ever/never), packyears, drink-years, block group median household income in 1999 (obtained from census data), and ambient or indoor air pollution (if applicable). Stratified analyses were performed by the potential effect modifiers, such as histologic types, gender, and smoking status. Relative risks (RR) and 95% confidence intervals (CI) are reported. Analyses were performed in SAS 9.4 (Cary, NC).

4.3 Results

A total of 577 lung cancer cases, 565 UADT cancers cases, and 983 combined controls eligible in this study are included in this study and their characteristics are presented in Table 4-1. Briefly, cancer patients had higher smoking packyears, drank more alcohol, less likely to receive college or higher degree, and more likely to be in the other race/ethnicity group. Lung cancer patients had even higher smoking prevalence and longer smoking packyears, while UADT cancer cases had longer alcohol drinking drink-years and were more likely to be males.

Table 4-2 shows the association between air pollution, measured as ambient $PM_{2.5}$ one-year before diagnosis, household air pollution (HAP, measured as exposure to solid fuel or ETS after adulthood), and air pollution index (API), and lung and UADT cancers susceptibility.

After adjusting for potential confounders, a slight increase of 2% in lung cancer risk was observed associated with each 1-$\mu g/m^3$ increase in ambient $PM_{2.5}$ concentration one-year before diagnosis, with a odds ratio (OR) of 1.02 and 95% confidence interval (CI) from 0.98 to 1.06, when comparing to the combined controls. People residing in areas experiencing the highest tertile (> 20.9 $\mu g/m^3$) of $PM_{2.5}$ concentration had elevated risk in lung cancer with an OR of 1.12 (95% CI: 0.82, 1.54), comparing to the first tertile ($PM_{2.5}$ concentration ≤ 17.9 $\mu g/m^3$). This association was not observed among people living in the second tertile (17.9 < $PM_{2.5}$ concentration ≤ 20.9 $\mu g/m^3$), with an OR of 0.98 (95% CI: 0.72, 1.33). When using controls originally matched to UADT cases (UADT controls), the results were similar. The association was consistent after stratifying by histologic types (Table 4-3). However, the association between each 1-$\mu g/m^3$ increase in ambient $PM_{2.5}$ concentration and lung cancer susceptibility were enhanced a little bit among males (OR = 1.06, 95% CI: 1.00, 1.12) comparing to females (OR = 0.98, 95% CI: 0.93, 1.04). Both the second tertile (OR = 1.07, 95% CI: 0.68, 1.67) and the highest tertile (OR = 1.49, 95% CI: 0.95, 2.33) showed increased risk in lung cancer susceptibility among males, but not among females (Table 4-9). After stratifying by smoking status, nonsmokers experienced a 6% increase in lung cancer risk associated with 1-$\mu g/m^3$ increase in ambient $PM_{2.5}$ (OR = 1.06, 95% CI: 0.98, 1.15), while the association tended to be null (OR = 1.00, 95% CI: 0.96, 1.05) for those who ever smoked (Table 4-15). However, the interactions between $PM_{2.5}$ and smoking seemed to be null on the multiplicative scale (Table 4-21).

The association between lung cancer susceptibility and HAP (OR = 0.87, 95% CI: 0.67, 1.14) and API (OR = 0.82, 95% CI: 0.58, 1.18) seemed to be null, even showing inverse associations, after adjusting for potential confounders (Table 4-3). After stratifying by histologic types, HAP

remained independent from lung cancer susceptibility, other than among those with squamous cell carcinoma, with an OR of 1.17 (95% CI: 0.65, 2.12) (Table 4-5). API seemed to be associated with increased risk in large cell carcinoma (OR = 1.14, 95% CI: 0.51, 2.55), but inversely associated with the small cell lung cancer risk (OR = 0.46, 95% CI:0.21, 1.01) (Table 4-7). Exposure to HAP seemed to be inversely associated with lung cancer susceptibility among males (OR = 0.71, 95% CI: 0.49, 1.03) and such association seemed to be null among females (OR = 1.06, 95% CI: 0.72, 1.58) (Table 4-11). Gender did not alter the association between lung cancer risk and API (Table 4-13). Nonsmoker (OR for HAP = 1.14, 95% CI: 0.68, 1.89; OR for API = 1.21, 95% CI: 0.63, 2.31) tended to be more vulnerable from HAP or any source of air pollution than smokers (OR for HAP = 0.78, 95% CI: 0.57, 1.08; OR for API = 0.69, 95% CI: 0.44, 1.08) (Table 4-17 and Table 4-19).

After adjusting for potential confounders, an increase of 4% in UADT cancers risk was observed associated with each 1-$\mu g/m^3$ increase in ambient $PM_{2.5}$ concentration one-year before diagnosis, with an OR of 1.04 (95% CI: 1.00, 1.09), when comparing to the combined controls. After categorizing $PM_{2.5}$ into tertiles, both second tertile (OR = 1.37, 95% CI: 1.02, 1.86) and the highest tertile (OR = 1.69, 95% CI: 1.25, 2.29) were associated with increased risks in UADT cancers. Such associations were strengthened when using controls originally matched to lung cancer cases (lung controls) (Table 4-2). Similar patterns were observed when stratifying by different UADT subtypes (Table 4-4), by gender (Table 4-10), and by smoking status (Table 4-16). There is no evidence for interaction between $PM_{2.5}$ and smoking on the susceptibility of UADT cancers (Table 4-22).

Unlike lung cancer, exposure to HAP (OR = 1.09, 95% CI: 0.85, 1.39) and API (OR = 1.42, 95% CI: 0.99, 2.02) were associated with increase susceptibility in UADT cancers (Table 4-2). HAP

seemed to be a risk factor for head and neck cancers, but not for esophageal cancers (Table 4-6). The risk associated with API does not alter too much across different UADT subtypes (Table 4-8). When stratifying by gender, exposure to HAP was associated with UADT susceptibility among females (OR = 1.51, 95% CI: 0.95, 2.40), but not among males (OR = 0.94, 0.71, 1.27) (Table 4-12). Females also experienced more profound impact on UADT cancer risks due to API (OR = 2.70, 95% CI: 1.21, 6.03), comparing to males (OR = 1.16, 95% CI: 0.77, 1.74) (Table 4-14). Similar patterns were observed among nonsmokers (OR for HAP = 1.41, 95% CI: 0.95, 2.10; OR for API = 1.67, 95% CI: 0.95, 2.85) comparing to among smokers (OR for HAP = 0.92, 95% CI: 0.67, 1.25; OR for API = 1.27, 95% CI: 0.78, 2.06) (Table 4-18 and Table 4-20).

4.4 Discussion

In this population-based case-control study in Los Angeles (LA), we examined the association between both ambient and indoor air pollution and lung and UADT cancers susceptibility. Our results suggest that ambient $PM_{2.5}$ is associated with both lung and UADT cancers susceptibility.

Consistent with previous studies [125, 127-130, 137-139, 184], we observed increased risk of lung cancer susceptibility associated with ambient $PM_{2.5}$ exposure, but the 95% CI included the null. As a population-base case-control study in LA, the study location represents a more homogenous source of air pollutant emission comparing to studies across multiple study sites. Therefore, the magnitude of the association might not be comparable across studies, as shown by the large heterogeneity when pooling different studies [139]. Another California study, the California Teacher Study (CTS) did not conclude the association between lung cancer mortality and $PM_{2.5}$ among female teachers (HR = 0.95, 95% CI: 0.70, 1.28), since only 234 lung cancer

deaths were identified during their follow up [148]. Though different methods of exposure were applied, our findings also indicated that the OR of lung cancer associated with 1-$\mu g/m^3$ increase in $PM_{2.5}$ is 0.98 (95% CI: 0.93, 1.04) among 291 female lung cancer cases. In addition, the stronger association between $PM_{2.5}$ and lung cancer risks among nonsmokers were observed in the Nurses' Health Study [149] and the extended Harvard Six Cities Study [147]. Consistently, we also observed a marginally increase in cancer risks associated with $PM_{2.5}$ among nonsmokers, but not among people who ever smoked. However, we might lack power to conclude the potential interaction between $PM_{2.5}$ and smoking on the susceptibility of lung cancer.

The positive association between UADT cancers susceptibility support the findings reported by the ESCAPE cohort, though their 95% CI included the null [164]. The ESCAPE study also showed the association by histological types, that UADT squamous cell carcinoma (HR = 1.16 per 10-$\mu g/m^3$, 95% CI: 0.78, 1.72), but not UADT adenocarcinoma (HR = 0.55 per 10-$\mu g/m^3$, 95% CI: 0.09, 3.50), was associated with $PM_{2.5}$ [160]. In a recent study using the SEER data, positive associations also were reported in different subsites, including oral (Incidence rate ratios (IRR) = 1.18, 95% CI: 1.03, 1.36), esophagus (IRR = 1.08, 95% CI: 0.88, 1.32), and larynx (IRR = 1.19, 95% CI: 0.97, 1.46), but not in cancer occurred in nose (IRR = 0.57, 95% CI: 0.35, 0.93) [184]. However, both nasopharyngeal cancer and oral cancer were associated with higher level of $PM_{2.5}$ in Taiwan [165, 166]. In our study, no obvious difference was observed between different subsites of UADT cancers due to the limited sample size but support the positive association among UADT squamous cell carcinoma.

Exposure to HAP since adulthood, combining solid fuel used for heating or cooking and ETS, was categorized into a binary variable. The data collected were without accounting for exposure intensity and duration, which might be vulnerable to potential measurement error, leading to

spurious observation of the associations between HAP and lung and UADT cancers, as reported by other studies previously [155, 157-160, 162, 163, 168-176, 178, 179, 185]. In addition, only very small proportion of participants were exposed to solid fuel used for heating or cooking during adulthood in our study, therefore the results of exposure to HAP were mainly over-weighted by the exposure to ETS. After stratifying by smoking status, there seems to be a positive association between exposure to HAP and both cancer types among nonsmokers, however, the association remained null among smokers possibly due to a very strong effect of active smoking on both cancers. The slight increase in lung cancer risk among females associated with HAP during adulthood supports the observation that the association between household ETS and lung cancer was more profound among females [163]. However, our study lacks power to make a solid conclusion when stratifying by smoking status and by genders.

There are several limitations in our study. Though we used different control sets to access the association between air pollution and lung and UADT cancers susceptibility, the results might still be vulnerable to selection bias due to the overmatching based on residential neighborhood. Such bias tends to attenuate the observed association towards the null due to lack of variation, leading underestimation. In such a case, the associations observed in our study should be conservative estimations. In addition, we could not rule out the possibility of measurement error, as discussed briefly before for the HAP measurement. Since we only have participants' residential addresses at diagnosis or on the reference date, we could not accurately estimate the long-term ambient $PM_{2.5}$ concentration and we assumed that the moving pattern was nondifferential between cases and controls before diagnosis or the reference date. Due to the availability of $PM_{2.5}$, we could only apply a 1-year lag between exposure assessment and cancer diagnosis, which might not be sufficient given the long latency of cancer development.

Moreover, the air pollution index was intended to show the increase in susceptibility associated with additional source of air pollution based on the additive effect. It might be hard to interpret, but at least we could use a simple index to quantify overall effect of both ambient and indoor air pollution. Though we tried to adjust for potential confounders at individual and block group level, there still might be possibility of residual or unknown confounding. Sample size might also be an issue to detect associations in some subgroup analyses. False positive findings might be resulted due to multiple comparisons. In addition, the $PM_{2.5}$ concentration is relatively high during the recruitment period of this study, comparing to current air pollution level in the LA county, which increased our chance to detection the association with our outcomes.

Nonetheless, our study is one of the earliest studies to investigate both ambient and household air pollution at the same time and its association with lung and UADT cancers susceptibility in the LA county and highlights the importance of improving air quality to reduce the susceptibility of lung and UADT cancers.

CHAPTER 5. CONCLUSIONS AND PUBLIC HEALTH IMPLICATIONS

Table 5-1 summarizes methods and findings of this study. In conclusion, this study suggests that air pollution is associated with both COVID-19 incidence, and lung and UADT cancers susceptibility. Ambient air pollution, the most widely spread carcinogen [55], may affect diseases via a variety of mechanisms such as altering immune response, increasing oxidative stress, causing inflammatory injury, inducing mutagenicity, and introducing respiratory tract damage [51-53]. It is also associated with adverse health effects, such as lung cancer, diseases in respiratory symptoms, including asthma and pneumonia, cardiovascular disease, preterm birth, low-birth weight, and emergency and hospital admission [54], as well as various infectious outcomes [56, 68-70]. However, individuals had little control over the ambient air pollution. Therefore, government and environmental agencies should set up proper public policy and regulations and enforce the policy implementation, which are essential to protect citizens from adverse effects associated with elevated $PM_{2.5}$ and to reduce the burden of healthcare systems, especially during an emerging outbreak, as we observed at the beginning of the SARS-CoV-2 pandemic. Thus, our results underscore the health hazards associated with ambient $PM_{2.5}$, which may be crucial for policymaking and program planning for improving air quality.

In addition, this study also adds evidence to the associations between $PM_{2.5}$ exposure and lung and UADT cancers susceptibility, highlighting the importance of identifying environmental factors. While future studies should verify the present associations, the interaction between environmental risk factors, including $PM_{2.5}$, and established risk factors for lung and UADT cancers, such as smoking and alcohol use, should also be examined for a better understanding of lung and UADT cancers etiology. Thus, effective prevention strategies to reduce lung and UADT cancers incidence can be developed for public health promotion.

Moreover, state-level non-pharmacologic prevention initiatives, such as facemask mandates and stay home orders, were effective in slowing down the spread of the SARS-CoV-2 during the first two surges of the COVID-19 pandemic. Though vaccine waning and breakthrough cases were observed, the protective effect of county-level cumulative complete vaccine coverages during the Alpha predominance and the protection from increasing booster coverages during the Omicron predominance highlight the importance to keep vaccine status up-to-date and suggest the 'spillover' effect to other individuals in the community. Hence, our results suggest that though not complied by every individual in the community, non-pharmacologic prevention interventions and increased up-to-date vaccination coverage still protect the community from COVID-19. This may be helpful in better preparation for the next surge of COVID-19 outbreak and even for the next emerging pandemic in the future.

TABLES

Table 1-1. Overview of Gaps in Literature

	COVID-19 in the US		Lung cancer	UADT cancers
	Incidence	Mortality	Susceptibility	Susceptibility
Long-term ambient $PM_{2.5}$	Few	-	Yes	Few
interact with smoking	-	-	Few	No
Facemask mandates	No	-	-	-
modify the association with $PM_{2.5}$	No			
Stay home orders	No	-	-	-
modify the association with $PM_{2.5}$	No			
Vaccine coverage	No	No	-	-
by dominant variant strains	No	No	-	-

Table 2-1. Literature Review on Air Pollution and COVID-19

Study Area	Study Period	Statistical Model	Findings
Northern Italy [73]	February 24th, 2020 – March 13th, 2020	Recursive binary partitioning tree approach	Daily PM_{10} exceeding 50 $\mu g/m^3$ with a 15-day lag was a significant predictor for COVID-19 incidence
Chinese cities (Wuhan, Xiaogan and Huanggang) [74]	January 25th, 2020– February 29th, 2020	Poison regression adjusting for other air pollutants and meteorological variables in each city	Daily $PM_{2.5}$ was positively associated with COVID-19 incidence with RR from 1.036 to 1.144. The association with PM_{10} was negative with RR between 0.915 and 0.964. Results for other pollutants (SO_2, CO, NO_2, and 8-hour O_3) were not consistent among the study sites.
Chinese cities (Wuhan and Xiaogan) [75]	January 26th, 2020– February 29th, 2020	Univariate linear regression	$PM_{2.5}$ and NO_2 were positively associated with COVID-19 incidence 4 days later in both cities, while PM_{10} and CO were inconsistent between cities.
120 Chinese cities [76]	January 23rd, 2020– February 29th, 2020	Generalized additive model adjusting for meteorological variables with city fixed effects	$PM_{2.5}$, PM_{10}, NO_2 and O_3 with a 2-week lag were positively associated with COVID-19 incidence, while SO_2 was negatively associated. A 10$\mu g/m^3$ increase in $PM_{2.5}$ with a 2-week lag was associated with a 2.24% increase in COVID-19 incidence.
49 Chinese cities [77]	As of March 22nd, 2020	Multivariate linear regression model adjusting for GDP per capita and hospital beds per capita	Both short-term (01/15/2020 – 02/29/2020) and long-term (2015–2019) exposure to elevated $PM_{2.5}$ and PM_{10} were associated with increased COVID-19 fatality. A 0.24% and a 0.61% increase in COVID-19 fatality were associated with 10-$\mu g/m^3$ increase in short-term and long-term $PM_{2.5}$, respectively.
7 metropolitan cities and 9 provinces in Korea [78]	February 3rd, 2020–May 5th, 2020	Generalized additive model adjusting for meteorological variables, location and date	Significantly temporal associations were observed between COVID-19 incidence and daily NO_2, CO and SO_2, but not with $PM_{2.5}$, PM_{10} or O_3.
3089 counties in the United States [79]	As of June 18th, 2020	Negative binomial fixed model adjusting for 20 covariates	Each 1-$\mu g/m^3$ increase in long-term $PM_{2.5}$ exposure (2000–2016 annual average) was associated with 11% increase in COVID-19 mortality.

Table 2-1. Literature Review on Air Pollution and COVID-19 (continued)

Study Area	Study Period	Statistical Model	Findings
3223 counties in the United States [80]	As of July 11th, 2020	Negative binomial fixed model adjusting for other pollutants as well as county characteristics	HAPs was associated with increase COVID-19 mortality. Each 1-$\mu g/m^3$ increase in long-term $PM_{2.5}$ exposure (2000–2014 annual average) was associated with 7% increase in COVID-19 mortality
355 municipalities in the Netherlands [81]	As of June 5th, 2020	Linear regression controlling for covariates	Long-term exposure to $PM_{2.5}$ and NO_2 were positively associated with COVID-19 outcomes, including incidence and mortality, but not with SO_2. Each 1-$\mu g/m^3$ increase in long-term $PM_{2.5}$ exposure (2015–2019) was associated with 9.4 more COVID-19 cases, 3.0 more hospital admissions, and 2.3 more deaths.
71 Italian provinces [82]	As of April 27th, 2020	Spatial correlation	Positive correlations were observed between COVID-19 incidence and long-term exposure (2016–2019) to NO_2, $PM_{2.5}$, PM_{10} and O_3.
20 Italian regions and up to 110 provinces [83]	As of March 31st, 2020	Multiple linear regression	Both long-term exposure (2017 annual mean) to $PM_{2.5}$ and PM_{10} were associated with COVID-19 incidence. Each 1-$\mu g/m^3$ increase in $PM_{2.5}$ was associated with 0.26 increase in base-10 transformed COVID-19 incidence.
3108 counties in the United States [84]	As of May 31st, 2020	Linear regression with adjusting for county-level covariates	$PM_{2.5}$ (2016 annual mean) and diesel PM were associated with both COVID-19 incidence and mortality. Additional 23.5 cases and 1.08 deaths were associated with each 1-$\mu g/m^3$ increase in $PM_{2.5}$.

Table 2-2. Summary of data sources

Sources	Description
Johns Hopkins University Center for Systems Science and Engineering Coronavirus Resource Center (CSSE)[13]	Cumulative county-level confirmed cases and deaths up to September 12th, 2020
GitHub repository by Wu et al. [79]	Annual average $PM_{2.5}$ concentration between 2000 and 2016
The US Census/American Community Survey	County-level socioeconomic and demographic variables in 2016
The County Health Rankings & Roadmaps program[86]	Country-level behavioral variables and rural/urban status in 2020
Boston University of Public Health[63]	State-level policy of face masks mandates and stay home orders before September 12th, 2020
The COVID tracking project [88]	State-level total tests performed
The New York Times [87]	State-level reopening policies

Table 2-3. Characteristics of Counties (*n* = 3,096) by COVID-19 Risk

County Characteristics	Total (*n* = 3,096) Mean (SD)	COVID risk ≤1.29% (*n* = 1,548) Mean (SD)	COVID risk >1.29% (*n* = 1,548) Mean (SD)
Risk of COVID-19 as of 9/12 (%)	1.65 (1.60)	0.69 (0.34)	2.62 (1.78)
Average ambient $PM_{2.5}$ ($\mu g/m^3$) [1]	8.40 (2.52)	7.49 (2.49)	9.32 (2.20)
Days since first case reported	163 (28)	156 (35)	170 (17)
Total test results reported by state (1000 tests)	2333 (2394)	2114 (2415)	2553 (2353)
Duration of stay at home issued by state	48 (40)	54 (44)	41 (35)
State stay-home order [2], *n* (%)			
Ever issued	2659 (85.89)	1312 (84.75)	1347 (87.02)
Never issued	437 (14.11)	236 (15.25)	201 (12.98)
State facemask policy [2], *n* (%)			
Ever issued	1853 (59.85)	964 (62.27)	889 (57.43)
Never issued	1243 (40.15)	584 (37.73)	659 (42.57)
State reopening status, *n* (%)			
Reopened	1225 (39.57)	815 (52.65)	410 (26.49)
Reopening	580 (18.73)	248 (16.02)	332 (21.45)
Pausing or reversing reopening plan	1291 (41.70)	485 (31.33)	806 (52.07)
Population density per square mile	427.39 (2184.38)	201.44 (720.43)	653.34 (2987.47)
African Americans population (%)	8.02 (14.07)	2.14 (5.07)	13.89 (17.35)
Hispanic Americans population (%)	7.54 (12.28)	5.14 (8.61)	9.94 (14.69)
Population living in poverty (%)	10.46 (5.90)	9.39 (5.36)	11.54 (6.20)
Population over 65 years old (%)	18.43 (4.50)	19.85 (4.28)	17.01 (4.27)

[1] Annual average of $PM_{2.5}$ between 2000 and 2016.
[2] State stay-home order and facemask mandates ever issued before 12 September 2020.

Table 2-3. Characteristics of Counties (*n* = 3096) by COVID-19 Risk (continued)

County Characteristics	Total (*n* = 3096) Mean (SD)	COVID risk ≤1.29% (*n* = 1548) Mean (SD)	COVID risk >1.29% (*n* = 1548) Mean (SD)
Male (%)	50.07 (2.20)	50.25 (1.93)	49.90 (2.43)
Population with less than high school education (%)	21.28 (10.68)	18.23 (9.53)	24.32 (10.90)
Owner occupied properties (%)	74.92 (8.41)	77.05 (6.94)	72.80 (9.18)
Median house value ($1000)	136.31 (91.08)	137.13 (88.39)	135.49 (93.71)
Median household income ($1000)	49.30 (13.41)	50.04 (11.87)	48.57 (14.75)
Ever smokers (%)	17.43 (3.54)	16.95 (3.44)	17.92 (3.57)
Obesity (%)	32.86 (5.41)	32.11 (5.09)	33.61 (5.62)

[1] Annual average of $PM_{2.5}$ between 2000 and 2016.
[2] State stay-home order and facemask mandates ever issued before 12 September 2020.

Table 2-4. Adjusted relative risks of COVID19 associated with 1-μg/m^3 increase in $PM_{2.5}$, facemask policy and stay home policy

	RR (95% CI) (95% CI with robust SE)		
	Surge 1 (as of May 28th, 2020)[3]	**Surge 2 (between May 29th and September 12th, 2020)[4]**	**Cumulative (as of September 12th, 2020)[4]**
$PM_{2.5}$[1], per μg/m^3	1.0506 (1.0269, 1.0747) (0.9857, 1.1197)	1.0852 (1.0696, 1.1011) (1.0361, 1.1366)	1.0756 (1.0612, 1.0901) (1.0376, 1.1149)
Facemask policy[2]			
Never issued		Reference	
Ever issued	0.9889 (0.9180, 1.0652) (0.8667, 1.1283)	0.8360 (0.8030, 0.8704) (0.7298, 0.9577)	0.8466 (0.8166, 0.8776) (0.7598, 0.9432)
Stay home policy[2]			
Never issued		Reference	
Ever issued	0.7615 (0.6928, 0.8370) (0.5619, 1.0321)	0.9168 (0.8664, 0.9701) (0.7833, 1.0730)	0.9193 (0.8734, 0.9677) (0.8021, 1.0537)

[1]Model 1 adjusts for population density, poverty, education, proportions of African Americans, proportions of Hispanic Americans, owner occupied property, median house value, median household income, smoking prevalence, obesity prevalence, population over 65 years old, gender, days since first case reported, total test results, duration of safer at home policy, facemask policy, and reopening status.
[2]Model 2 adjusts for all covariates in model 1 + incidence of COVID19 up to 14 days prior (May 14th, 2020 for surge 1 and August 28th, 2020 for surge 2 and cumulative) and $PM_{2.5}$.
[3]State stay-home order and facemask mandates ever issued before May 28th, 2020.
[4]State stay-home order and facemask mandates ever issued before September 12th, 2020.

Table 2-5. Adjusted relative risks of COVID-19 associated with 1-μg/m^3 increase in $PM_{2.5}$ by facemask policy and by stay home policy.

	RR (95% CI) (95% CI with robust SE) Surge 1 (as of May 28th, 2020)[4]	Surge 2 (between May 28th and September 12th, 2020)[5]	Cumulative (as of September 12th, 2020)[5]
Face mask policy[1]			
Never issued	1.0426 (1.0144, 1.0717) (0.9645, 1.1270)	1.0417 (1.0165, 1.0675) (0.9905, 1.0955)	1.0547 (1.0293, 1.0807) (1.0109, 1.1004)
Ever issued	1.0854 (1.0327, 1.1407) (0.9817, 1.2000)	1.1161 (1.0958, 1.1368) (1.0640, 1.1708)	1.0852 (1.0673, 1.1034) (1.0420, 1.1301)
Stay home policy			
Never issued[2]	1.4050 (1.2885, 1.5319) (1.2961, 1.5230)	1.1056 (1.0406, 1.1746) (1.0478, 1.1665)	1.1543 (1.0870, 1.2257) (1.1016, 1.2095)
Ever issued[3]	1.0186 (0.9947, 1.0431) (0.9565, 1.0848)	1.0970 (1.0803, 1.1140) (1.0441, 1.1526)	1.0798 (1.0648, 1.0949) (1.0386, 1.1226)

[1]Model 1 adjusts for population density, poverty, education, proportions of African Americans, proportions of Hispanic Americans, owner occupied property, median house value, median household income, smoking prevalence, obesity prevalence, population over 65 years old, gender, days since first case reported, total test results, duration of safer at home policy, and reopening status.
[2]Model 2 adjusts for population density, poverty, education, proportions of African Americans, proportions of Hispanic Americans, owner occupied property, median house value, median household income, smoking prevalence, obesity prevalence, population over 65 years old, gender, days since first case reported, total test results, facemask policy, and reopening status.
[3]Model 3 adjusts for all covariates in model 2 + duration of safer at home.
[4]State stay-home order and facemask mandates ever issued before May 28th,2020.
[5]State stay-home order and facemask mandates ever issued before September 12th, 2020.

Table 3-1. Summary of data sources

Sources	Description
Johns Hopkins University Center for Systems Science and Engineering Coronavirus Resource Center (CSSE) [13]	Cumulative county-level confirmed cases and deaths up to March 25, 2022
Covid Act Now [122]	Cumulative county-level number of people completely vaccinated and number of completed vaccinated people receiving booster up to March 11, 2022
Atmospheric Composition Analysis Group [85]	Annual average $PM_{2.5}$ concentration between 2000 and 2018
The US Census/American Community Survey	County-level socioeconomic and demographic variables in 2020
The County Health Rankings & Roadmaps program [86]	Country-level behavioral variables and rural/urban status in 2020
Boston University of Public Health [63]	State-level policy of face masks mandates and stay home orders before July 2nd, 2022

Table 3-2. Characteristics of counties (n = 3,073) in 48 states as of March 25th, 2022

	All	Mean (SD) Vaccination rate ≤ 49.8% as of March 11th, 2022	Vaccination rate > 49.8% as of March 11th, 2022
No. of county in No. of states	3,073 in 48 states	1,542 in 40 states	1,531 in 48 states
Incidence of COVID-19 as of 3/25/2022[1], %	24.22 (5.70)	24.35 (5.66)	24.08 (5.73)
Incidence of COVID-19 as of 12/1/2021[1], %	15.96 (3.98)	16.67 (3.80)	15.24 (4.03)
Incidence of COVID-19 as of 7/2/2021[1], %	10.22 (3.07)	10.54 (2.93)	9.92 (3.16)
Mortality of COVID-19 as of 3/25/2022[2], %	0.36 (0.16)	0.41 (0.16)	0.31 (0.15)
Mortality of COVID-19 as of 12/1/2021[2], %	0.28 (0.14)	0.32 (0.14)	0.24 (0.13)
Mortality of COVID-19 as of 7/2/2021[2], %	0.20 (0.11)	0.22 (0.11)	0.18 (0.11)
Full vaccination rate as of 3/11/2022[3], %	50.79 (11.90)	42.48 (6.00)	60.17 (8.54)
Full vaccination rate as of 2/25/2022[3], %	50.45 (11.83)	41.19 (5.96)	59.77 (8.48)
Full vaccination rate as of 11/17/2021[3], %	44.51 (12.13)	35.92 (7.87)	53.17 (9.13)
Full vaccination rate as of 11/3/2021[3], %	43.85 (12.32)	35.03 (8.17)	52.26 (9.33)
Full vaccination rate as of 6/18/2021[3], %	32.06 (11.06)	24.82 (7.67)	38.99 (9.21)
Full vaccination rate as of 6/4/2021[3], %	30.24 (10.64)	23.46 (7.62)	36.81 (8.89)
Booster rate as of 3/11/2022[3], %	22.41 (8.24)	17.07 (4.16)	28.18 (7.65)
Booster rate as of 2/25/2022[3], %	21.91 (8.12)	16.68 (4.12)	27.57 (7.57)
Average ambient $PM_{2.5}$[4], $\mu g/m^3$	7.86 (2.18)	7.92 (2.16)	7.80 (2.19)
Ever smokers, %	17.48 (3.56)	18.32 (3.36)	16.63 (3.54)
Adult obesity, %	32.90 (5.42)	33.94 (5.01)	31.85 (5.61)
Population living in poverty, %	14.66 (6.18)	15.82 (5.90)	13.49 (6.24)
Population density, No. per square mile	206.44 (916.43)	59.56 (111.88)	354.38 (1276.72)

[1]COVID-19 cases out of total population in each county
[2]COVID-19 deaths out of total population in each county
[3]Number of people fully vaccinated out of total population of all age groups in each county
[4]Annual average of $PM_{2.5}$ between 2000 and 2018

Table 3-2. Characteristics of counties (n = 3,073) in 48 states as of March 25th, 2022 (continued)

	All	Mean (SD) Vaccination rate ≤ 49.8% as of March 11th, 2022	Vaccination rate > 49.8% as of March 11th, 2022
Owner occupied properties, %	72.08 (8.22)	73.18 (7.23)	70.97 (8.98)
Adults with less than high school education, %	12.74 (5.80)	14.33 (5.60)	11.13 (5.55)
White Americans population, %	77.05 (17.58)	79.63 (15.88)	74.45 (18.78)
African Americans population, %	8.83 (14.21)	8.56 (13.96)	11.04 (14.45)
Hispanic population, %	9.72 (13.63)	8.41 (11.59)	9.11 (15.31)
Median house value, ×$1,000	25.22 (66.44)	8.56 (10.31)	42.00 (90.52)
Median household income, ×$1,000	68.30 (16.73)	62.19 (11.42)	74.46 (18.84)
Population over 65 years old, %	19.28 (4.72)	19.54 (4.34)	19.02 (5.07)
Male, %	50.05 (2.38)	50.27 (2.65)	49.82 (2.05)
Uninsured population, %	9.48 (5.04)	10.81 (4.96)	8.14 (4.76)
Population living in rural, %	58.53 (31.38)	69.28 (26.18)	47.67 (32.46)
State stay-home order before 7/2/2021, n (%)			
Ever issued	2192 (71.33)	1013 (65.69)	1179 (77.01)
Never issued	881 (28.67)	529 (34.31)	352 (22.99)
State facemask policy before 7/2/2021, n (%)			
Ever issued	2299 (74.81)	991 (64.27)	1308 (85.43)
Never issued	774 (25.19)	551 (35.73)	223 (14.57)

[a]COVID-19 cases out of total population in each county
[b]COVID-19 deaths out of total population in each county
[c]Number of people fully vaccinated out of total population of all age groups in each county
[d]Annual average of $PM_{2.5}$ between 2000 and 2018

Table 3-3. Adjusted relative risks of COVID-19 incidence and mortality associated with additional people fully vaccinated and with additional people receiving a booster dose per 100 population between April 23rd, 2021 and March 25th, 2022 stratified by the most dominant variant

	Relative Risk (95% Confidence Interval)		
Dominant variant	Alpha (April 23rd – July 2nd, 2021)	Delta (July 3rd – December 1st, 2021)	Omicron (December 2nd, 2021 – March 25th, 2022)
Incidence[1]			
Fully vaccinated (n = 3,073 in 48 states)	0.9607 (0.9553, 0.9661)	0.9988 (0.9964, 1.0011)	0.9969 (0.9919, 1.0019)
Booster (n = 2,906 in 46 states)	N/A	N/A	0.9356 (0.9235, 0.9479)
Mortality[2]			
Fully vaccinated (n = 3,042 in 48 states)	0.9694 (0.9653, 0.9736)	0.9934 (0.9889, 0.9980)	1.0061 (1.0022, 1.0101)
Booster (n = 2,876 in 46 states)	N/A	N/A	0.9595 (0.9431, 0.9761)

[1]Model 1 adjusts for annual $PM_{2.5}$ concentration between 2000 and 2018, percentage of adults smokers, percentage of obese adults, percentage of people living under poverty, population density, percentage of owner occupied properties, percentage of adults with less than high school education, percentage of White population, median household income, median house value, percentage of population over 65 years old, percentage of male, percentage of population without an insurance, percentage of population living in rural area, stay home orders before July 2nd, 2021 (ever/never) and facemask mandate before July 2nd, 2021 (ever/never); fully vaccination rate and booster rate were assessed two weeks prior the end of each period

[2]Model 2 adjusts for all covariates in model 1; fully vaccination rate and booster rate were assessed four weeks prior the end of each period

Table 4-1. Characteristics (n = 2,125) by cancer status

	Combined controls	Lung cancer cases	UADT cancers controls[1]	UADT cancer cases	Lung cancer controls[1]
Total no. of subjects	983	577	448	565	535
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
$PM_{2.5}$ concentration 1 year before diagnosis, $\mu g/m^3$	18.81 (3.26)	18.97 (3.21)	18.90 (3.24)	19.30 (3.16)	18.74 (3.29)
Age, year	49.85 (7.30)	52.25 (5.39)	48.82 (8.33)	50.42 (7.57)	50.64 (6.21)
Smoking, packyears	9.84 (16.35)	31.56 (25.27)	10.15 (16.15)	22.91 (24.28)	9.58 (16.53)
Alcohol drinking, drink-years	28.93 (61.98)	55.20 (136.44)	32.53 (65.29)	100.06 (202.31)	25.91 (58.97)
Block group median household income in 1999, $1,000 dollar	54.07 (25.60)	51.96 (25.93)	53.98 (26.23)	51.04 (24.35)	54.98 (25.05)
	N (%)	N (%)	N (%)	N (%)	N (%)
Gender					
Male	585 (59.51)	286 (49.57)	330 (73.66)	426 (75.40)	255 (47.66)
Female	398 (40.49)	291 (50.43)	118 (26.34)	139 (24.60)	280 (52.34)
Education					
Less than high school	115 (11.70)	104 (18.02)	51 (11.38)	125 (22.12)	64 (11.96)
High school	178 (18.11)	150 (26.00)	71 (15.85)	138 (24.42)	107 (20.00)
Some college	266 (27.06)	175 (30.33)	127 (28.35)	147 (26.02)	139 (25.98)
College	191 (19.43)	81 (14.04)	84 (18.75)	93 (16.46)	107 (20.00)
Graduate school	233 (23.70)	67 (11.61)	115 (25.67)	62 (10.97)	118 (22.06)
Race/Ethnicity					
Non-Hispanic White	587 (59.72)	333 (57.71)	268 (59.82)	314 (55.58)	319 (59.63)
African American	98 (9.97)	94 (16.29)	43 (9.60)	68 (12.04)	55 (10.28)
Hispanic	201 (20.45)	68 (11.79)	93 (20.76)	108 (19.12)	108 (20.19)
Other	97 (9.87)	82 (14.21)	44 (9.82)	75 (13.27)	53 (9.91)

[1]Controls originally matched to UADT cancers were used to assess the susceptibility of lung cancer and controls originally matched to lung cancer were used to assess the susceptibility of UADT cancer

[2]Solid fuel for heating includes fireplace, wood, coal, oil and kerosene

[3]Solid fuel for cooing includes charcoal, wood, and coal stove

Table 4-1. Characteristics (n = 2,125) by cancer status (continued)

	Combined controls	Lung cancer cases	UADT cancers controls[1]	UADT cancer cases	Lung cancer controls[1]
Total no. of subjects	983	577	448	565	535
Smoking					
Never	445 (45.27)	101 (17.50)	198 (44.20)	164 (29.03)	247 (46.17)
Ever	538 (54.73)	476 (82.50)	250 (55.80)	401 (70.97)	288 (53.83)
Solid fuel[2] for heating since adulthood					
No	967 (98.37)	566 (98.09)	437 (97.54)	558 (98.76)	530 (99.07)
Yes	16 (1.63)	11 (1.91)	11 (2.46)	7 (1.24)	5 (0.93)
Solid fuel[2] for cooking since adulthood					
No	982 (99.90)	574 (99.48)	448 (100.00)	557 (98.58)	534 (99.81)
Yes	1 (0.10)	3 (0.52)	0 (0.00)	8 (1.42)	1 (0.19)
Exposure to environmental tobacco smoking since adulthood					
No	469 (47.71)	202 (35.01)	223(49.78)	229 (40.53)	246 (45.98)
Yes	514 (52.29)	375 (64.99)	225 (50.22)	336 (59.47)	289 (54.02)
Exposure to solid fuel or ETS since adulthood					
No	459 (46.69)	195 (33.80)	216 (48.21)	221 (39.12)	243 (45.42)
Any	524 (53.31)	328 (66.20)	232 (51.79)	344 (60.88)	292 (54.58)

[1]Controls originally matched to UADT cancers were used to assess the susceptibility of lung cancer and controls originally matched to lung cancer were used to assess the susceptibility of UADT cancer
[2]Solid fuel for heating includes fireplace, wood, coal, oil and kerosene
[3]Solid fuel for cooing includes charcoal, wood, and coal stove

Table 4-2. Associations between air pollution and lung and upper aerodigestive track cancers susceptibility

Variable	Lung cancer, N (%)	Combined controls, N (%)	Adjusted OR (95% CI)	UADT cancers controls[1], N (%)	Adjusted OR (95% CI)	UADT cancers, N (%)	Combined controls, N (%)	Adjusted OR (95% CI)	Lung cancer controls[1], N (%)	Adjusted OR (95% CI)
$PM_{2.5}$ concentration one-year before diagnosis[2,3]										
Per $\mu g/m^3$	577 (100.00)	983 (100.00)	1.02 (0.98, 1.06)	448 (100.00)	1.02 (0.97, 1.07)	565 (100.00)	983 (100.00)	1.04 (1.00, 1.09)	535 (100.00)	1.04 (1.00, 1.09)
Below median	258 (44.71)	486 (49.44)	Reference	222 (49.55)	Reference	240 (42.48)	486 (49.44)	Reference	264 (49.35)	Reference
Above median	319 (55.29)	497 (50.56)	1.18 (0.91, 1.53)	226 (50.45)	1.24 (0.90, 1.72)	325 (57.52)	497 (50.56)	1.32 (1.04, 1.69)	271 (50.65)	1.27 (0.96, 1.70)
Tertile 1	185 (32.06)	331 (33.67)	Reference	141 (31.47)	Reference	144 (25.49)	331 (33.67)	Reference	190 (35.51)	Reference
Tertile 2	196 (33.97)	327 (33.27)	0.98 (0.72, 1.33)	156 (34.82)	0.89 (0.60, 1.31)	191 (33.81)	327 (33.27)	1.37 (1.02, 1.86)	171 (31.96)	1.52 (1.07, 2.15)
Tertile 3	196 (33.97)	325 (33.06)	1.12 (0.82, 1.54)	151 (33.71)	1.05 (0.71, 1.56)	230 (40.71)	325 (33.06)	1.69 (1.25, 2.29)	174 (32.52)	1.79 (1.26, 2.54)
p-value for trend			0.46		0.79			< 0.01		< 0.01

[1]Controls originally matched to UADT cancers were used to assess the susceptibility of lung cancer and controls originally matched to lung cancer were used to assess the susceptibility of UADT cancer

[2]Models adjust for age, gender, education, race/ethnicity, smoking (ever/never), packyears, drink-years, block group median household income in 1999, and ambient or indoor air pollution (if applicable)

[3]$PM_{2.5}$ concentration among combined controls: below median ($\leq$ 19.1 $\mu g/m^3$) and above median (> 19.1 $\mu g/m^3$); tertile 1 ($\leq$ 17.9 $\mu g/m^3$), tertile 2 (17.9 < $PM_{2.5} \leq$ 20.9 $\mu g/m^3$), and tertile 3(> 20.9 $\mu g/m^3$)

[4]Air pollution index was computed based on exposure to any source of household air pollution since adulthood, including solid fuels for cooking or heating and environmental tobacco smoking (yes = 1, no =0) and exposure to ambient air pollution (Tertile 1 = 0, Tertile 2 = 1, Tertile 3 = 2)

Table 4-2. Associations between air pollution and lung and upper aerodigestive track cancers susceptibility (continued)

Variable	Lung cancer, N (%)	Combined controls, N (%)	Adjusted OR (95% CI)	UADT controls[1], N (%)	Adjusted OR (95% CI)	UADT cancers, N (%)	Combined controls, N (%)	Adjusted OR (95% CI)	Lung controls[1], N (%)	Adjusted OR (95% CI)
Exposure to household air pollution, including solid fuels or ETS since adulthood[2]										
No	195 (33.80)	459 (46.69)	Reference	216 (48.21)	Reference	221 (39.12)	459 (46.69)	Reference	243 (45.42)	Reference
Any	382 (66.20)	524 (53.31)	0.87 (0.67, 1.14)	232 (51.79)	0.80 (0.57, 1.11)	344 (60.88)	524 (53.31)	1.09 (0.85, 1.39)	292 (54.58)	1.14 (0.86, 1.52)
Air pollution index[2,3]										
0	68 (11.79)	157 (15.97)	Reference	69 (15.40)	Reference	58 (10.27)	157 (15.97)	Reference	88 (16.45)	Reference
≥1	509 (88.21)	826 (84.03)	0.82 (0.58, 1.18)	379 (84.60)	0.68 (0.44, 1.07)	507 (89.73)	826 (84.03)	1.42 (0.99, 2.02)	447 (83.55)	1.50 (1.00, 2.25)
1	175 (30.33)	331 (33.67)	0.72 (0.49, 1.07)	152 (33.93)	0.60 (0.37, 0.98)	156 (27.61)	331 (33.67)	1.15 (0.78, 1.69)	179 (33.46)	1.20 (0.77, 1.87)
2	207 (35.88)	315 (32.04)	0.93 (0.63, 1.37)	143 (31.92)	0.79 (0.48, 1.29)	214 (37.88)	315 (32.04)	1.58 (1.07, 2.33)	172 (32.15)	1.67 (1.07, 2.60)
3	127 (22.01)	180 (18.31)	0.85 (0.55, 1.31)	84 (18.75)	0.69 (0.40, 1.18)	137 (24.25)	180 (18.31)	1.75 (1.15, 2.67)	96 (17.94)	1.96 (1.20, 3.18)
P-value for trend			0.93		0.60			< 0.01		< 0.01

[1]Controls originally matched to UADT cancers were used to assess the susceptibility of lung cancer and controls originally matched to lung cancer were used to assess the susceptibility of UADT cancer

[2]Models adjust for age, gender, education, race/ethnicity, smoking (ever/never), packyears, drink-years, block group median household income in 1999, and the ambient or indoor air pollution (if applicable)

[3]$PM_{2.5}$ concentration among combined controls: below median (≤ 19.1 μg/m^3) and above median (> 19.1 μg/m^3); tertile 1 (≤ 17.9 μg/m^3), tertile 2 (17.9 < $PM_{2.5}$ ≤ 20.9 μg/m^3), and tertile 3(> 20.9 μg/m^3)

[4]Air pollution index was computed based on exposure to any source of household air pollution since adulthood, including solid fuels for cooking or heating and environmental tobacco smoking (yes = 1, no =0) and exposure to ambient air pollution (Tertile 1 = 0, Tertile 2 = 1, Tertile 3 = 2)

Table 4-3. Associations between $PM_{2.5}$ concentration[1] one-year before diagnosis and lung cancer susceptibility by histologic types

Cancer type	Cases, N (%)	Combined controls, N (%)	Adjusted OR[2] (95% CI)	UADT controls[3], N (%)	Adjusted OR[2] (95% CI)
Non-small cell lung cancer (n = 476)					
Per $\mu g/m^3$	476 (100.00)	983 (100.00)	1.02 (0.98, 1.06)	448 (100.00)	1.01 (0.96, 1.7)
Below median	212 (44.54)	486 (49.44)	Reference	222 (49.55)	Reference
Above median	264 (55.46)	497 (50.56)	1.21(0.92, 1.59)	226 (50.45)	1.26 (0.90, 1.77)
Tertile 1	151 (31.72)	331 (33.67)	Reference	141 (31.47)	Reference
Tertile 2	164 (34.45)	327 (33.27)	0.98 (0.71, 1.36)	156 (34.82)	0.88 (0.59, 1.32)
Tertile 3	161 (33.82)	325 (33.06)	1.13 (0.81, 1.57)	151 (33.71)	1.03 (0.68, 1.56)
p-value for trend			0.46		0.87
Squamous cell carcinoma (n = 90)					
Per $\mu g/m^3$	90 (100.00)	983 (100.00)	1.05 (0.95, 1.15)	448 (100.00)	1.02 (0.91, 1.13)
Below median	40 (44.44)	486 (49.44)	Reference	222 (49.55)	Reference
Above median	50 (55.56)	497 (50.56)	0.96 (0.55, 1.70)	226 (50.45)	0.91 (0.48, 1.75)
Tertile 1	21 (23.33)	331 (33.67)	Reference	141 (31.47)	Reference
Tertile 2	37 (41.11)	327 (33.27)	1.20 (0.60, 2.40)	156 (34.82)	1.02 (0.47, 2.25)
Tertile 3	32 (35.56)	325 (33.06)	1.55 (0.77, 3.11)	151 (33.71)	1.07 (0.48, 2.42)
p-value for trend			0.21		0.86

[1]$PM_{2.5}$ concentration among combined controls: below median ($\leq 19.1\ \mu g/m^3$) and above median ($> 19.1\ \mu g/m^3$); tertile 1 ($\leq 17.9\ \mu g/m^3$), tertile 2 ($17.9 < PM_{2.5} \leq 20.9\ \mu g/m^3$), and tertile 3($> 20.9\ \mu g/m^3$)

[2]Models adjust for age, gender, education, race/ethnicity, smoking (ever/never), packyears, drink-years, block group median household income in 1999, and household air pollution since adulthood

[3]Controls originally matched to UADT cancers were used to assess the susceptibility of lung cancer

Table 4-3. Associations between $PM_{2.5}$ concentration[1] one-year before diagnosis and lung cancer susceptibility by histologic types (continued)

Cancer type	Cases, N (%)	Combined controls, N (%)	Adjusted OR[2] (95% CI)	UADT controls[3], N (%)	Adjusted OR[2] (95% CI)
Adenocarcinoma (n = 282)					
Per μg/m^3	282 (100.00)	983 (100.00)	1.02 (0.97, 1.07)	448 (100.00)	1.02 (0.96, 1.08)
Below median	124 (43.97)	486 (49.44)	Reference	222 (49.55)	Reference
Above median	158 (56.03)	497 (50.56)	1.35 (0.99, 1.85)	226 (50.45)	1.39 (0.95, 2.03)
Tertile 1	100 (35.46)	331 (33.67)	Reference	141 (31.47)	Reference
Tertile 2	92 (32.62)	327 (33.27)	0.93 (0.64, 1.35)	156 (34.82)	0.89 (0.57, 1.39)
Tertile 3	90 (31.91)	325 (33.06)	1.13 (0.81, 1.57)	151 (33.71)	0.99 (0.63, 1.57)
p-value for trend			0.78		0.97
Large cell carcinoma (n = 104)					
Per μg/m^3	104 (100.00)	983 (100.00)	1.00 (0.92, 1.08)	448 (100.00)	0.98 (0.90, 1.07)
Below median	48 (46.15)	486 (49.44)	Reference	222 (49.55)	Reference
Above median	56 (53.85)	497 (50.56)	0.92 (0.56, 1.53)	226 (50.45)	0.88 (0.49, 1.60)
Tertile 1	30 (28.85)	331 (33.67)	Reference	141 (31.47)	Reference
Tertile 2	35 (33.65)	327 (33.27)	0.92 (0.50, 1.68)	156 (34.82)	0.78 (0.39, 1.56)
Tertile 3	39 (37.50)	325 (33.06)	1.27 (0.70, 2.31)	151 (33.71)	1.00 (0.49, 2.00)
p-value for trend			0.41		0.99

[1]$PM_{2.5}$ concentration among combined controls: below median (≤ 19.1 μg/m^3) and above median (> 19.1 μg/m^3); tertile 1 (≤ 17.9 μg/m^3), tertile 2 (17.9 < $PM_{2.5}$ ≤ 20.9 μg/m^3), and tertile 3(> 20.9 μg/m^3)

[2]Models adjust for age, gender, education, race/ethnicity, smoking (ever/never), packyears, drink-years, block group median household income in 1999, and household air pollution since adulthood

[3]Controls originally matched to UADT cancers were used to assess the susceptibility of lung cancer

Table 4-3. Associations between $PM_{2.5}$ concentration[1] one-year before diagnosis and lung cancer susceptibility by histologic types (continued)

Cancer type	Cases, N (%)	Combined controls, N (%)	Adjusted OR[2] (95% CI)	UADT controls[3], N (%)	Adjusted OR[2] (95% CI)
Small cell lung cancer (n = 72)					
Per μg/m^3	72 (100.00)	983 (100.00)	1.01 (0.92, 1.11)	448 (100.00)	1.00 (0.89, 1.12)
Below median	31 (43.06)	486 (49.44)	Reference	222 (49.55)	Reference
Above median	41 (56.94)	497 (50.56)	1.07 (0.59, 1.95)	226 (50.45)	0.99 (0.48, 2.03)
Tertile 1	21 (29.17)	331 (33.67)	Reference	141 (31.47)	Reference
Tertile 2	27 (37.50)	327 (33.27)	1.10 (0.55, 2.21)	156 (34.82)	0.96 (0.42, 2.17)
Tertile 3	24 (33.33)	325 (33.06)	1.12 (0.55, 2.39)	151 (33.71)	0.81 (0.33, 2.00)
p-value for trend			0.71		0.65

[1]$PM_{2.5}$ concentration among combined controls: below median (≤ 19.1 μg/m^3) and above median (> 19.1 μg/m^3); tertile 1 (≤ 17.9 μg/m^3), tertile 2 (17.9 < $PM_{2.5}$ ≤ 20.9 μg/m^3), and tertile 3(> 20.9 μg/m^3)

[2]Models adjust for age, gender, education, race/ethnicity, smoking (ever/never), packyears, drink-years, block group median household income in 1999, and household air pollution since adulthood

[3]Controls originally matched to UADT cancers were used to assess the susceptibility of lung cancer

Table 4-4. Associations between $PM_{2.5}$ concentration[1] one-year before diagnosis and upper aerodigestive track cancers susceptibility by histologic types

Cancer type	Cases, N (%)	Combined controls, N (%)	Adjusted OR[2] (95% CI)	Lung controls[3], N (%)	Adjusted OR[2] (95% CI)
UADT squamous cell carcinoma (n = 413)					
Per μg/m^3	413 (100.00)	983 (100.00)	1.04 (1.00, 1.09)	535 (100.00)	1.04 (1.00, 1.09)
Below median	176 (42.62)	486 (49.44)	Reference	264 (49.35)	Reference
Above median	237 (57.38)	497 (50.56)	1.34 (1.02, 1.75)	271 (50.65)	1.29 (0.95, 1.74)
Tertile 1	104 (25.18)	331 (33.67)	Reference	190 (35.51)	Reference
Tertile 2	142 (34.38)	327 (33.27)	1.38 (0.99, 1.91)	171 (31.96)	1.48 (1.02, 2.16)
Tertile 3	167 (40.44)	325 (33.06)	1.71 (1.23, 2.38)	174 (32.52)	1.81 (1.24, 2.63)
p-value for trend			< 0.01		< 0.01
Oropharyngeal squamous cell carcinoma (n = 320)					
Per μg/m^3	320 (100.00)	983 (100.00)	1.03 (0.99, 1.08)	535 (100.00)	1.03 (0.98, 1.08)
Below median	138 (43.13)	486 (49.44)	Reference	264 (49.35)	Reference
Above median	182 (56.88)	497 (50.56)	1.33 (0.99, 1.19)	271 (50.65)	1.27 (0.92, 1.76)
Tertile 1	83 (25.94)	331 (33.67)	Reference	190 (35.51)	Reference
Tertile 2	112 (35.00)	327 (33.27)	1.34 (0.93, 1.93)	171 (31.96)	1.44 (0.96, 2.15)
Tertile 3	125 (39.06)	325 (33.06)	1.65 (1.15, 2.36)	174 (32.52)	1.73 (1.15, 2.59)
p-value for trend			< 0.01		< 0.01

[1]$PM_{2.5}$ concentration among combined controls: below median (≤ 19.1 μg/m^3) and above median (> 19.1 μg/m^3); tertile 1 (≤ 17.9 μg/m^3), tertile 2 (17.9 < $PM_{2.5}$ ≤ 20.9 μg/m^3), and tertile 3(> 20.9 μg/m^3)

[2]Models adjust for age, gender, education, race/ethnicity, smoking (ever/never), packyears, drink-years, block group median household income in 1999, and household air pollution since adulthood

[3]Controls originally matched to UADT cancers were used to assess the susceptibility of lung cancer

Table 4-4. Associations between $PM_{2.5}$ concentration[1] one-year before diagnosis and upper aerodigestive track cancers susceptibility by histologic types (continued)

Cancer type	Cases, N (%)	Combined controls, N (%)	Adjusted OR[2] (95% CI)	Lung controls[3], N (%)	Adjusted OR[2] (95% CI)
Nasopharyngeal squamous cell carcinoma (n = 46)					
Per μg/m^3	46 (100.00)	983 (100.00)	1.08 (0.96, 1.21)	535 (100.00)	1.06 (0.94, 1.21)
Below median	18 (39.13)	486 (49.44)	Reference	264 (49.35)	Reference
Above median	28 (60.87)	497 (50.56)	1.07 (0.54, 2.15)	271 (50.65)	0.97 (0.46, 2.04)
Tertile 1	9 (19.57)	331 (33.67)	Reference	190 (35.51)	Reference
Tertile 2	10 (21.74)	327 (33.27)	0.98 (0.36, 2.66)	171 (31.96)	0.92 (0.32, 2.69)
Tertile 3	27 (58.70)	325 (33.06)	2.07 (0.86, 4.97)	174 (32.52)	2.11 (0.82, 5.46)
p-value for trend			0.06		0.07
Esophageal squamous cell carcinoma (n = 32)					
Per μg/m^3	46 (100.00)	983 (100.00)	1.10 (0.95, 1.28)	535 (100.00)	1.11 (0.95, 1.29)
Below median	15 (46.88)	486 (49.44)	Reference	264 (49.35)	Reference
Above median	17 (53.13)	497 (50.56)	0.98 (0.41, 2.37)	271 (50.65)	1.04 (0.42, 2.59)
Tertile 1	7 (21.88)	331 (33.67)	Reference	190 (35.51)	Reference
Tertile 2	15 (46.88)	327 (33.27)	2.30 (0.82, 6.42)	171 (31.96)	2.60 (0.86, 7.86)
Tertile 3	10 (31.25)	325 (33.06)	1.50 (0.47, 4.72)	174 (32.52)	1.81 (0.54, 6.05)

[1]$PM_{2.5}$ concentration among combined controls: below median (≤ 19.1 μg/m^3) and above median (> 19.1 μg/m^3); tertile 1 (≤ 17.9 μg/m^3), tertile 2 (17.9 < $PM_{2.5}$ ≤ 20.9 μg/m^3), and tertile 3(> 20.9 μg/m^3)

[2]Models adjust for age, gender, education, race/ethnicity, smoking (ever/never), packyears, drink-years, block group median household income in 1999, and household air pollution since adulthood

[3]Controls originally matched to UADT cancers were used to assess the susceptibility of lung cancer

Table 4-4. Associations between $PM_{2.5}$ concentration[1] one-year before diagnosis and upper aerodigestive track cancers susceptibility by histologic types (continued)

Cancer type	Cases, N (%)	Combined controls, N (%)	Adjusted OR[2] (95% CI)	Lung controls[3], N (%)	Adjusted OR[2] (95% CI)
Esophageal adenocarcinoma (n = 68)					
Per $\mu g/m^3$	68 (100.00)	983 (100.00)	1.05 (0.96, 1.14)	535 (100.00)	1.04 (0.95, 1.14)
Below median	33 (48.53)	486 (49.44)	Reference	264 (49.35)	Reference
Above median	35 (51.47)	497 (50.56)	1.18 (0.67, 2.05)	271 (50.65)	1.07 (0.59, 1.95)
Tertile 1	20 (29.41)	331 (33.67)	Reference	190 (35.51)	Reference
Tertile 2	20 (29.41)	327 (33.27)	1.19 (0.57, 2.38)	171 (31.96)	1.30 (0.62, 2.72)
Tertile 3	28 (41.18)	325 (33.06)	1.72 (0.88, 3.37)	174 (32.52)	1.84 (0.89, 3.79)
p-value for trend			0.11		0.10

[1]$PM_{2.5}$ concentration among combined controls: below median ($\leq 19.1\ \mu g/m^3$) and above median ($> 19.1\ \mu g/m^3$); tertile 1 ($\leq 17.9\ \mu g/m^3$), tertile 2 ($17.9 < PM_{2.5} \leq 20.9\ \mu g/m^3$), and tertile 3($> 20.9\ \mu g/m^3$)

[2]Models adjust for age, gender, education, race/ethnicity, smoking (ever/never), packyears, drink-years, block group median household income in 1999, and household air pollution since adulthood

[3]Controls originally matched to UADT cancers were used to assess the susceptibility of lung cancer

Table 4-5. Associations between exposure to solid fuel or environmental tobacco smoking since adulthood and lung cancer susceptibility by histologic types

Cancer type	Cases, N (%)	Combined controls, N (%)	Adjusted OR[1] (95% CI)	UADT controls[2], N (%)	Adjusted OR[1] (95% CI)
Non-small cell lung cancer (n = 476)					
No	164 (34.45)	459 (46.69)	Reference	216 (48.21)	Reference
Any	312 (65.55)	524 (53.31)	0.91 (0.69, 1.20)	232 (51.79)	0.82 (0.58, 1.16)
Squamous cell carcinoma (n = 90)					
No	26 (28.89)	459 (46.69)	Reference	216 (48.21)	Reference
Any	64 (71.11)	524 (53.31)	1.17 (0.65, 2.12)	232 (51.79)	1.03 (0.53, 1.99)
Adenocarcinoma (n = 282)					
No	102 (36.17)	459 (46.69)	Reference	216 (48.21)	Reference
Any	180 (63.83)	524 (53.31)	0.98 (0.71, 1.35)	232 (51.79)	0.87 (0.59, 1.28)
Large cell carcinoma (n = 104)					
No	36 (34.62)	459 (46.69)	Reference	216 (48.21)	Reference
Any	68 (65.38)	524 (53.31)	0.76 (0.46, 1.27)	232 (51.79)	0.64 (0.35, 1.15)
Small cell lung cancer (n =72)					
No	20 (27.78)	459 (46.69)	Reference	216 (48.21)	Reference
Any	52 (72.22)	524 (53.31)	0.90 (0.48, 1.69)	232 (51.79)	0.62 (0.29, 1.29)

[1]Models adjust for age, gender, education, race/ethnicity, smoking (ever/never), packyears, drink-years, block group median household income in 1999, and $PM_{2.5}$ concentration one year before diagnosis

[2]Controls originally matched to UADT cancers were used to assess the susceptibility of lung cancer

Table 4-6. Associations between exposure to solid fuel or environmental tobacco smoking since adulthood and upper aerodigestive track cancers incidence by histologic types

Cancer type	Cases, N (%)	Combined controls, N (%)	Adjusted OR[1] (95% CI)	Controls for Lung Cancer[2], N (%)	Adjusted OR[1] (95% CI)
UADT squamous cell carcinoma (n = 413)					
No	159 (38.50)	459 (46.69)	Reference	243 (45.42)	Reference
Any	254 (61.50)	524 (53.31)	1.19 (0.91, 1.55)	292 (54.58)	1.24 (0.91, 1.69)
Oropharyngeal squamous cell carcinoma (n = 320)					
No	122 (38.13)	459 (46.69)	Reference	243 (45.42)	Reference
Any	198 (61.88)	524 (53.31)	1.13 (0.84, 1.51)	292 (54.58)	1.18 (0.84, 1.65)
Nasopharyngeal squamous cell carcinoma (n = 46)					
No	17 (36.96)	459 (46.69)	Reference	243 (45.42)	Reference
Any	29 (63.04)	524 (53.31)	1.90 (0.94, 3.83)	292 (54.58)	1.85 (0.87, 3.96)
Esophageal squamous cell carcinoma (n = 32)					
No	15 (46.88)	459 (46.69)	Reference	243 (45.42)	Reference
Any	17 (53.13)	524 (53.31)	0.50 (0.22, 1.13)	292 (54.58)	0.51 (0.21, 1.25)
Esophageal adenocarcinoma (n = 68)					
No	28 (41.18)	459 (46.69)	Reference	243 (45.42)	Reference
Any	40 (58.82)	524 (53.31)	0.86 (0.49, 1.51)	292 (54.58)	0.87 (0.48, 1.58)

[1]Models adjust for age, gender, education, race/ethnicity, smoking (ever/never), packyears, drink-years, block group median household income in 1999, and $PM_{2.5}$ concentration one year before diagnosis

[2]Controls originally matched to lung cancer were used to assess the susceptibility of UADT cancer

Table 4-7. Associations between air pollution index[1] and lung cancer susceptibility by histologic types

Cancer type	Cases, N (%)	Combined controls, N (%)	Adjusted OR[2] (95% CI)	UADT controls[3], N (%)	Adjusted OR[2] (95% CI)
Non-small cell lung cancer (n = 476)					
0	53 (11.13)	157 (15.97)	Reference	69 (15.40)	Reference
≥1	423 (88.87)	826 (84.03)	0.90 (0.62, 1.33)	379 (84.60)	0.72 (0.45, 1.16)
1	152 (31.93)	331 (33.67)	0.84 (0.55, 1.27)	152 (33.93)	0.68 (0.40, 1.14)
2	167 (35.08)	315 (32.04)	0.95 (0.62, 1.44)	143 (31.92)	0.76 (0.45, 1.29)
3	104 (21.85)	180 (18.31)	0.97 (0.61, 1.52)	84 (18.75)	0.75 (0.42, 1.33)
P-value for trend			0.78		0.63
Squamous cell carcinoma (n = 90)					
0	7 (7.78)	157 (15.97)	Reference	69 (15.40)	Reference
≥1	83 (88.21)	826 (84.03)	0.89 (0.37, 2.14)	379 (84.60)	0.69 (0.25, 1.90)
1	24 (26.67)	331 (33.67)	0.64 (0.24, 1.70)	152 (33.93)	0.67 (0.22, 2.00)
2	36 (40.00)	315 (32.04)	0.93 (0.35, 2.31)	143 (31.92)	0.58 (0.20, 1.74)
3	23 (25.56)	180 (18.31)	1.29 (0.49, 3.42)	84 (18.75)	0.94 (0.30, 2.94)
P-value for trend			0.17		0.84
Adenocarcinoma (n = 282)					
0	38 (13.48)	157 (15.97)	Reference	69 (15.40)	Reference
≥1	244 (86.52)	826 (84.03)	0.85 (0.56, 1.29)	379 (84.60)	0.70 (0.42, 1.16)
1	92 (32.62)	331 (33.67)	0.77 (0.49, 1.23)	152 (33.93)	0.63 (0.36, 1.10)
2	96 (34.04)	315 (32.04)	0.90 (0.57, 1.43)	143 (31.92)	0.75 (0.43, 1.32)
3	56 (19.86)	180 (18.31)	0.93 (0.56, 1.55)	84 (18.75)	0.74 (0.40, 1.38)
P-value for trend			0.85		0.69

[1]Air pollution index was computed based on exposure to any source of household air pollution since adulthood, including solid fuels for cooking or heating and environmental tobacco smoking (yes = 1, no =0) and exposure to ambient air pollution (Tertile 1 = 0, Tertile 2 = 1, Tertile 3 = 2)
[2]Models adjust for age, gender, education, race/ethnicity, smoking (ever/never), packyears, drink-years, and block group median household income in 1999
[3]Controls originally matched to UADT cancers were used to assess the susceptibility of lung cancer

Table 4-7. Associations between air pollution index[1] and lung cancer susceptibility by histologic types (continued)

Cancer type	Cases, N (%)	Combined controls, N (%)	Adjusted OR[2] (95% CI)	UADT controls[3], N (%)	Adjusted OR[2] (95% CI)
Large cell carcinoma (n = 104)					
0	8 (7.69)	157 (15.97)	Reference	69 (15.40)	Reference
≥1	96 (92.31)	826 (84.03)	1.14 (0.51, 2.55)	379 (84.60)	0.87 (0.34, 2.21)
1	36 (34.62)	331 (33.67)	1.20 (0.51, 2.83)	152 (33.93)	1.02 (0.38, 2.74)
2	35 (33.65)	315 (32.04)	1.06 (0.44, 2.52)	143 (31.92)	0.75 (0.27, 2.06)
3	25 (24.04)	180 (18.31)	1.19 (0.48, 2.96)	84 (18.75)	0.80 (0.28, 2.33)
P-value for trend			0.88		0.45
Small cell lung cancer (n = 72)					
0	10 (13.89)	157 (15.97)	Reference	69 (15.40)	Reference
≥1	62 (86.11)	826 (84.03)	0.46 (0.21, 1.01)	379 (84.60)	0.31 (0.12, 0.79)
1	14 (19.44)	331 (33.67)	0.24 (0.09, 0.63)	152 (33.93)	0.20 (0.07, 0.62)
2	31 (43.06)	315 (32.04)	0.70 (0.30, 1.63)	143 (31.92)	0.44 (0.16, 1.22)
3	17 (23.61)	180 (18.31)	0.51 (0.19, 1.30)	84 (18.75)	0.29 (0.09, 0.91)
P-value for trend			0.88		0.27

[1]Air pollution index was computed based on exposure to any source of household air pollution since adulthood, including solid fuels for cooking or heating and environmental tobacco smoking (yes = 1, no =0) and exposure to ambient air pollution (Tertile 1 = 0, Tertile 2 = 1, Tertile 3 = 2)
[2]Models adjust for age, gender, education, race/ethnicity, smoking (ever/never), packyears, drink-years, and block group median household income in 1999
[3]Controls originally matched to UADT cancers were used to assess the susceptibility of lung cancer

Table 4-8. Associations between air pollution index[1] and upper aerodigestive track cancer susceptibility by histologic types

Cancer type	Cases, N (%)	Combined controls, N (%)	Adjusted OR[2] (95% CI)	Lung controls[3], N (%)	Adjusted OR[2] (95% CI)
UADT squamous cell carcinoma (n = 413)					
0	45 (10.90)	157 (15.97)	Reference	88 (16.45)	Reference
≥1	368 (89.10)	826 (84.03)	1.45 (0.98, 2.13)	447 (83.55)	1.53 (0.99, 2.36)
1	109 (26.39)	331 (33.67)	1.12 (0.73, 1.72)	179 (33.46)	1.16 (0.72, 1.88)
2	156 (37.77)	315 (32.04)	1.63 (1.07, 2.48)	172 (32.15)	1.70 (1.06, 2.74)
3	103 (24.94)	180 (18.31)	1.86 (1.18, 2.93)	96 (17.94)	2.07 (1.24, 3.48)
P-value for trend			< 0.01		< 0.01
Oropharyngeal squamous cell carcinoma (n = 320)					
0	37 (11.56)	157 (15.97)	Reference	88 (16.45)	Reference
≥1	283 (88.44)	826 (84.03)	1.28 (0.85, 1.94)	447 (83.55)	1.32 (0.83, 2.08)
1	81 (25.31)	331 (33.67)	0.96 (0.60, 1.52)	179 (33.46)	0.96 (0.58, 1.61)
2	127 (39.69)	315 (32.04)	1.54 (0.98, 2.42)	172 (32.15)	1.55 (0.94, 2.56)
3	75 (23.44)	180 (18.31)	1.56 (0.95, 2.57)	96 (17.94)	1.74 (0.99, 3.03)
P-value for trend			< 0.01		< 0.01
Nasopharyngeal squamous cell carcinoma (n = 46)					
0	4 (8.70)	157 (15.97)	Reference	88 (16.45)	Reference
≥1	42 (91.30)	826 (84.03)	-	447 (83.55)	-
1	9 (19.57)	331 (33.67)	-	179 (33.46)	-
2	15 (32.61)	315 (32.04)	-	172 (32.15)	-
3	18 (39.13)	180 (18.31)	-	96 (17.94)	-
P-value for trend			-		-

[1]Air pollution index was computed based on exposure to any source of household air pollution since adulthood, including solid fuels for cooking or heating and environmental tobacco smoking (yes = 1, no =0) and exposure to ambient air pollution (Tertile 1 = 0, Tertile 2 = 1, Tertile 3 = 2)
[2]Models adjust for age, gender, education, race/ethnicity, smoking (ever/never), packyears, drink-years, and block group median household income in 1999
[3]Controls originally matched to UADT cancers were used to assess the susceptibility of lung cancer

Table 4-8. Associations between air pollution index[1] and upper aerodigestive track cancer susceptibility by histologic types (continued)

Cancer type	Cases, N (%)	Combined controls, N (%)	Adjusted OR[2] (95% CI)	Lung controls[3], N (%)	Adjusted OR[2] (95% CI)
Esophageal squamous cell carcinoma (n = 32)					
0	3 (9.38)	157 (15.97)	Reference	88 (16.45)	Reference
≥1	29 (90.63)	826 (84.03)	-	447 (83.55)	-
1	12 (37.50)	331 (33.67)	-	179 (33.46)	-
2	11 (34.38)	315 (32.04)	-	172 (32.15)	-
3	6 (18.75)	180 (18.31)	-	96 (17.94)	-
P-value for trend			-		-
Esophageal adenocarcinoma (n = 68)					
0	8 (11.76)	157 (15.97)	Reference	88 (16.45)	Reference
≥1	60 (88.24)	826 (84.03)	1.08 (0.49, 2.41)	447 (83.55)	1.11 (0.48, 2.56)
1	19 (27.94)	331 (33.67)	0.80 (0.33, 1.96)	179 (33.46)	0.80 (0.56, 2.05)
2	26 (38.24)	315 (32.04)	1.37 (0.58, 3.27)	172 (32.15)	1.40 (0.19, 3.51)
3	15 (22.06)	180 (18.31)	1.26 (0.49, 3.26)	96 (17.94)	1.38 (0.50, 3.79)
P-value for trend			0.27		0.22

[1]Air pollution index was computed based on exposure to any source of household air pollution (yes = 1, no =0) and exposure to ambient air pollution (Tertile 1 = 0, Tertile 2 = 1, Tertile 3 = 2)
[2]Models adjust for age, gender, education, race/ethnicity, smoking (ever/never), packyears, drink-years, and block group median household income in 1999
[3]Controls originally matched to lung cancer were used to assess the susceptibility of UADT cancer

Table 4-9. Associations between $PM_{2.5}$ concentration[1] one-year before diagnosis and lung cancers susceptibility by gender

	Cases, N (%)	Combined controls, N (%)	Adjusted OR[2] (95% CI)	UADT controls[3], N (%)	Adjusted OR[2] (95% CI)
Male					
Per $\mu g/m^3$	286 (100.00)	585 (100.00)	1.06 (1.00, 1.12)	330 (100.00)	1.08 (1.01, 1.16)
Below median	124 (43.36)	293 (50.09)	Reference	173 (52.42)	Reference
Above median	162 (56.64)	292 (49.91)	1.45 (1.00 2.11)	157 (47.58)	1.73 (1.12, 2.67)
Tertile 1	89 (31.12)	199 (34.02)	Reference	113 (34.24)	Reference
Tertile 2	92 (32.62)	190 (32.48)	1.07 (0.68, 1.67)	111 (33.64)	1.12 (0.97, 1.86)
Tertile 3	105 (36.71)	196 (33.50)	1.49 (0.95, 2.33)	106 (32.12)	1.58 (0.94, 2.67)
p-value for trend			0.07		0.08
Female					
Per $\mu g/m^3$	291 (100.00)	398 (100.00)	0.98 (0.93, 1.04)	118 (100.00)	0.94 (0.86, 1.02)
Per $\mu g/m^3$	134 (46.05)	193 (48.49)	Reference	49 (41.53)	Reference
Below median	157 (53.95)	205 (51.51)	0.99 (0.68, 1.43)	69 (58.47)	0.83 (0.49, 1.40)
Above median	96 (32.99)	132 (33.17)	Reference	28 (23.73)	Reference
Tertile 1	104 (35.74)	137 (34.42)	0.86 (0.55, 1.34)	45 (38.14)	0.60 (0.32, 1.16)
Tertile 2	91 (31.27)	129 (32.41)	0.85 (0.54, 1.34)	45 (38.14)	0.58 (0.30, 1.13)
p-value for trend			0.49		0.11

[1]$PM_{2.5}$ concentration among combined controls: below median ($\leq$ 19.1 $\mu g/m^3$) and above median (> 19.1 $\mu g/m^3$); tertile 1 ($\leq$ 17.9 $\mu g/m^3$), tertile 2 (17.9 < $PM_{2.5} \leq$ 20.9 $\mu g/m^3$), and tertile 3(> 20.9 $\mu g/m^3$)

[2]Models adjust for age, education, race/ethnicity, smoking (ever/never), packyears, drink-years, block group median household income in 1999, and the household air pollution

[3]Controls originally matched to UADT cancers were used to assess the susceptibility of lung cancer

Table 4-10. Associations between $PM_{2.5}$ concentration[1] one-year before diagnosis and upper aerodigestive track cancers susceptibility by gender

	Cases, N (%)	Combined controls, N (%)	Adjusted OR[2] (95% CI)	Lung controls[3], N (%)	Adjusted OR[2] (95% CI)
Male					
Per $\mu g/m^3$	426 (100.00)	585 (100.00)	1.04 (0.99, 1.09)	330 (100.00)	1.02 (0.97, 1.08)
Below median	186 (43.66)	293 (50.09)	Reference	173 (52.42)	Reference
Above median	240 (56.34)	292 (49.91)	1.35 (1.00 1.81)	157 (47.58)	1.17 (0.81, 1.68)
Tertile 1	116 (27.23)	199 (34.02)	Reference	113 (34.24)	Reference
Tertile 2	137 (32.16)	190 (32.48)	1.24 (0.86, 1.79)	111 (33.64)	1.28 (0.81, 2.01)
Tertile 3	173 (40.61)	196 (33.50)	1.70 (1.18, 2.45)	106 (32.12)	1.61 (1.03, 2.52)
p-value for trend			< 0.01		0.03
Female					
Per $\mu g/m^3$	139 (100.00)	398 (100.00)	1.05 (0.97, 1.13)	118 (100.00)	1.08 (1.00, 1.16)
Below median	54 (38.85)	193 (48.49)	Reference	49 (41.53	Reference
Above median	85 (61.15)	205 (51.51)	1.29 (0.83, 2.01)	69 (58.47)	1.45 (0.90, 2.33)
Tertile 1	28 (20.14)	132 (33.17)	Reference	28 (23.73)	Reference
Tertile 2	54 (38.85)	137 (34.42)	1.75 (1.00, 1.11)	45 (38.14)	2.17 (1.21, 3.91)
Tertile 3	57 (41.01)	129 (32.41)	1.76 (1.00, 3.10)	45 (38.14)	2.14 (1.16, 3.92)
p-value for trend			0.06		0.02

[1]$PM_{2.5}$ concentration among combined controls: below median ($\leq$ 19.1 $\mu g/m^3$) and above median (> 19.1 $\mu g/m^3$); tertile 1 ($\leq$ 17.9 $\mu g/m^3$), tertile 2 (17.9 < $PM_{2.5} \leq$ 20.9 $\mu g/m^3$), and tertile 3(> 20.9 $\mu g/m^3$)

[2]Models adjust for age, education, race/ethnicity, smoking (ever/never), packyears, drink-years, block group median household income in 1999, and the household air pollution

[3]Controls originally matched to lung cancer were used to assess the susceptibility of UADT cancer

Table 4-11. Associations between exposure to solid fuel or environmental tobacco smoking since adulthood and lung cancer susceptibility by gender

	Cases, N (%)	Combined controls, N (%)	Adjusted OR[1] (95% CI)	UADT controls[2], N (%)	Adjusted OR[1] (95% CI)
Male					
No	106 (37.06)	283 (48.38)	Reference	161 (48.89)	Reference
Any	180 (62.94)	302 (51.62)	0.71 (0.49, 1.03)	169 (51.21)	0.70 (0.46, 1.08)
Female					
No	89 (33.58)	176 (44.22)	Reference	55 (46.61)	Reference
Any	202 (69.42)	222 (55.78)	1.06 (0.72, 1.58)	63 (53.39)	0.88 (0.51, 1.53)

[1]Models adjust for age, education, race/ethnicity, smoking (ever/never), packyears, drink-years, block group median household income in 1999, and $PM_{2.5}$ concentration one year before diagnosis

[2]Controls originally matched to UADT cancers were used to assess the susceptibility of lung cancer

Table 4-12. Associations between exposure to solid fuel or environmental tobacco smoking since adulthood and upper aerodigestive track cancers susceptibility by gender

	Cases, N (%)	Combined controls, N (%)	Adjusted OR[1] (95% CI)	Lung controls[2], N (%)	Adjusted OR[1] (95% CI)
Male					
No	174 (40.85)	283 (48.38)	Reference	122 (47.84)	Reference
Any	252 (59.15)	302 (51.62)	0.94 (0.71, 1.27)	133 (52.16)	0.95 (0.66, 1.36)
Female					
No	47 (33.81)	176 (44.22)	Reference	121 (43.21)	Reference
Any	92 (66.19)	222 (55.78)	1.51 (0.95, 2.40)	159 (56.79)	1.58 (0.95, 2.62)

[1]Models adjust for age, education, race/ethnicity, smoking (ever/never), packyears, drink-years, block group median household income in 1999, and $PM_{2.5}$ concentration one year before diagnosis

[2]Controls originally matched to lung cancer were used to assess the susceptibility of UADT cancer

Table 4-13. Associations between air pollution index[1] and lung cancer susceptibility by gender

	Cases, N (%)	Combined controls, N (%)	Adjusted OR[2] (95% CI)	UADT controls[3], N (%)	Adjusted OR[2] (95% CI)
Male					
0	32 (11.19)	97 (16.58)	Reference	59 (17.88)	Reference
≥1	254 (88.81)	488 (83.42)	0.87 (0.53, 1.44)	271 (82.12)	0.95 (0.54, 1.66)
1	87 (30.42)	199 (34.02)	0.71 (0.41, 1.23)	113 (34.24)	0.76 (0.41, 1.41)
2	106 (37.06)	182 (31.11)	1.09 (0.63, 1.90)	95 (28.79)	1.27 (0.68, 2.39)
3	61 (21.33)	107 (18.29)	0.90 (0.49, 1.65)	63 (19.09)	0.91 (0.46, 1.81)
P-value for trend			0.60		0.59
Female					
0	36 (12.37)	60 (15.08)	Reference	10 (8.47)	Reference
≥1	255 (87.63)	338 (84.92)	0.80 (0.48, 1.33)	108 (91.53)	0.37 (0.16, 0.86)
1	88 (30.24)	132 (33.17)	0.78 (0.44, 1.37)	39 (33.05)	0.39 (0.16, 0.97)
2	101 (34.71)	133 (33.42)	0.81 (0.46, 1.42)	48 (40.68)	0.34 (0.14, 0.83)
3	66 (22.68)	73 (18.34)	0.82 (0.44, 1.53)	21 (17.80)	0.40 (0.15, 1.08)
P-value for trend			0.66		0.11

[1]Air pollution index was computed based on exposure to any source of household air pollution since adulthood, including solid fuels for cooking or heating and environmental tobacco smoking (yes = 1, no =0) and exposure to ambient air pollution (Tertile 1 = 0, Tertile 2 = 1, Tertile 3 = 2)

[2]Models adjust for age, education, race/ethnicity, smoking (ever/never), packyears, drink-years, and block group median household income in 1999

[3]Controls originally matched to UADT cancers were used to assess the susceptibility of lung cancer

Table 4-14. Associations between air pollution index[1] and upper aerodigestive cancer susceptibility by gender

	Cases, N (%)	Combined controls, N (%)	Adjusted OR[2] (95% CI)	Lung controls[3], N (%)	Adjusted OR[2] (95% CI)
Male					
0	50 (11.74)	97 (16.58)	Reference	38 (14.90)	Reference
≥1	376 (88.26)	488 (83.42)	1.16 (0.77, 1.74)	217 (85.10)	1.03 (0.62, 1.72)
1	115 (27.00)	199 (34.02)	0.89 (0.57, 1.41)	86 (33.73)	0.81 (0.46, 1.42)
2	163 (38.26)	182 (31.11)	1.39 (0.89, 2.19)	87 (34.12)	1.17 (0.67, 2.05)
3	98 (23.00)	107 (18.29)	1.39 (0.85, 2.29)	44 (17.25)	1.34 (0.72, 2.50)
P-value for trend			0.03		0.10
Female					
0	8 (5.76)	60 (15.08)	Reference	50 (17.86)	Reference
≥1	131 (94.24)	338 (84.92)	2.70 (1.21, 6.03)	230 (82.14)	3.65 (1.57, 8.46)
1	41 (29.50)	132 (33.17)	2.41 (1.02, 5.67)	93 (33.21)	3.02 (1.23, 7.39)
2	51 (36.69)	133 (33.42)	2.59 (1.11, 6.06)	85 (30.36)	3.90 (1.60, 9.55)
3	39 (28.06)	73 (18.34)	3.50 (1.44, 8.52)	52 (18.57)	4.58 (1.78, 11.70)
P-value for trend			< 0.01		< 0.01

[1]Air pollution index was computed based on exposure to any source of household air pollution since adulthood, including solid fuels for cooking or heating and environmental tobacco smoking (yes = 1, no =0) and exposure to ambient air pollution (Tertile 1 = 0, Tertile 2 = 1, Tertile 3 = 2)

[2]Models adjust for age, education, race/ethnicity, smoking (ever/never), packyears, drink-years, and block group median household income in 1999

[3]Controls originally matched to lung cancer were used to assess the susceptibility of UADT cancer

Table 4-15. Associations between $PM_{2.5}$ concentration[1] one-year before diagnosis and lung cancers susceptibility by smoking status

	Cases, N (%)	Combined controls, N (%)	Adjusted OR[2] (95% CI)	UADT controls[3], N (%)	Adjusted OR[2] (95% CI)
Nonsmokers					
Per $\mu g/m^3$	101 (100.00)	445 (100.00)	1.06 (0.98, 1.15)	198 (100.00)	1.07 (0.97, 1.17)
Below median	37 (36.63)	223 (50.11)	Reference	102 (51.52)	Reference
Above median	64 (63.37)	222 (49.89)	1.53 (0.92 2.56)	96 (48.48)	1.55 (0.84, 2.85)
Tertile 1	27 (26.73)	144 (32.36)	Reference	64 (32.32)	Reference
Tertile 2	30 (29.70)	155 (34.83)	1.12 (0.59, 2.12)	71 (35.86)	1.19 (0.55, 2.60)
Tertile 3	44 (43.56)	146 (32.81)	1.34 (0.73, 2.47)	63 (31.82)	1.46 (0.69, 3.07)
p-value for trend			0.33		0.31
Smokers					
Per $\mu g/m^3$	476 (100.00)	538 (100.00)	1.00 (0.96, 1.05)	250 (100.00)	1.00 (0.94, 1.07)
Below median	221 (46.43)	263 (48.88)	Reference	120 (48.00)	Reference
Above median	255 (53.57)	275 (51.12)	1.08 (0.79, 1.47)	130 (52.00)	1.11 (0.74, 1.66)
Tertile 1	158 (33.19)	187 (34.76)	Reference	77 (30.80)	Reference
Tertile 2	166 (34.87)	172 (31.97)	0.97 (0.68, 1.39)	85 (34.00)	0.86 (0.54, 1.38)
Tertile 3	152 (31.93)	179 (33.27)	1.08 (0.74, 1.57)	88 (35.20)	0.97 (0.59, 1.58)
p-value for trend			0.70		0.89

[1]$PM_{2.5}$ concentration among combined controls: below median ($\leq$ 19.1 $\mu g/m^3$) and above median (> 19.1 $\mu g/m^3$); tertile 1 ($\leq$ 17.9 $\mu g/m^3$), tertile 2 (17.9 < $PM_{2.5} \leq$ 20.9 $\mu g/m^3$), and tertile 3(> 20.9 $\mu g/m^3$)

[2]Models adjust for age, gender, education, race/ethnicity, drink-years, block group median household income in 1999, the household air pollution and packyears if applicable

[3]Controls originally matched to UADT cancers were used to assess the susceptibility of lung cancer

Table 4-16. Associations between $PM_{2.5}$ concentration[1] one-year before diagnosis and upper aerodigestive track cancers susceptibility by smoking status

	Cases, N (%)	Combined controls, N (%)	Adjusted OR[2] (95% CI)	UADT controls[3], N (%)	Adjusted OR[2] (95% CI)
Nonsmokers					
Per $\mu g/m^3$	164 (100.00)	445 (100.00)	1.03 (0.97, 1.10)	247 (100.00)	1.03 (0.96, 1.10)
Below median	68 (41.46)	223 (50.11)	Reference	121 (48.99)	Reference
Above median	96 (58.54)	222 (49.89)	1.28 (0.86, 1.91)	126 (51.01)	1.20 (0.76, 1.90)
Tertile 1	42 (25.61)	144 (32.36)	Reference	80 (32.39)	Reference
Tertile 2	52 (31.71)	155 (34.83)	1.27 (0.77, 2.10)	84 (34.01)	1.26 (0.72, 2.21)
Tertile 3	70 (42.68)	146 (32.81)	1.51 (0.92, 2.49)	83 (33.60)	1.44 (0.82, 2.53)
p-value for trend			0.11		0.21
Smokers					
Per $\mu g/m^3$	401 (100.00)	538 (100.00)	1.05 (1.00, 1.11)	288 (100.00)	1.06 (0.99, 1.12)
Below median	172 (42.89)	263 (48.88)	Reference	143 (49.65)	Reference
Above median	229 (57.11)	275 (51.12)	1.34 (0.98, 1.84)	145 (50.35)	1.31 (0.90, 1.90)
Tertile 1	102 (25.44)	187 (34.76)	Reference	110 (38.19)	Reference
Tertile 2	139 (34.66)	172 (31.97)	1.52 (1.04, 2.22)	87 (30.21)	1.83 (1.16, 2.87)
Tertile 3	160 (39.90)	179 (33.27)	1.83 (1.25, 2.69)	91 (31.60)	2.09 (1.33, 3.30)
p-value for trend			< 0.01		< 0.01

[1]$PM_{2.5}$ concentration among combined controls: below median ($\leq$ 19.1 $\mu g/m^3$) and above median (> 19.1 $\mu g/m^3$); tertile 1 ($\leq$ 17.9 $\mu g/m^3$), tertile 2 (17.9 < $PM_{2.5} \leq$ 20.9 $\mu g/m^3$), and tertile 3(> 20.9 $\mu g/m^3$)

[2]Models adjust for age, gender, education, race/ethnicity, drink-years, block group median household income in 1999, the household air pollution and packyears if applicable

[3]Controls originally matched to lung cancer were used to assess the susceptibility of UADT cancer

Table 4-17. Associations between exposure to solid fuel or environmental tobacco smoking since adulthood and lung cancer susceptibility by smoking status

	Cases, N (%)	Combined controls, N (%)	Adjusted OR[1] (95% CI)	UADT controls[2], N (%)	Adjusted OR[1] (95% CI)
Nonsmokers					
No	56 (55.45)	272 (61.12)	Reference	128 (64.65)	Reference
Any	45 (44.55)	173 (38.88)	1.14 (0.68, 1.89)	70 (35.35)	1.26 (0.68, 2.32)
Smokers					
No	139 (29.20)	187 (34.76)	Reference	88 (35.20)	Reference
Any	337 (70.80)	351 (65.24)	0.78 (0.57, 1.08)	162 (64.80)	0.63 (0.42, 0.96)

[1]Models adjust for age, gender, education, race/ethnicity, drink-years, block group median household income in 1999, $PM_{2.5}$ concentration one year before diagnosis and packyears if applicable

[2]Controls originally matched to UADT cancers were used to assess the susceptibility of lung cancer

Table 4-18. Associations between exposure to solid fuel or environmental tobacco smoking since adulthood and upper aerodigestive track cancers susceptibility by smoking status

	Cases, N (%)	Combined controls, N (%)	Adjusted OR[1] (95% CI)	Lung controls[2], N (%)	Adjusted OR[1] (95% CI)
Nonsmokers					
No	88 (53.66)	272 (61.12)	Reference	144 (58.30)	Reference
Any	76 (46.34)	173 (38.88)	1.41 (0.95, 2.10)	103 (41.70)	1.46 (0.93, 2.29)
Smokers					
No	133 (33.17)	187 (34.76)	Reference	99 (34.38)	Reference
Any	268 (66.83)	351 (65.24)	0.92 (0.67, 1.25)	189 (65.63)	0.96 (0.65, 1.39)

[1]Models adjust for age, gender, education, race/ethnicity, drink-years, block group median household income in 1999, $PM_{2.5}$ concentration one year before diagnosis and packyears if applicable

[2]Controls originally matched to lung cancer were used to assess the susceptibility of UADT cancer

Table 4-19. Associations between air pollution index[1] and lung cancer susceptibility by smoking status

	Cases, N (%)	Combined controls, N (%)	Adjusted OR[2] (95% CI)	UADT controls[3], N (%)	Adjusted OR[2] (95% CI)
Nonsmokers					
0	17 (16.83)	91 (20.45)	Reference	44 (22.22)	Reference
≥1	84 (83.17)	354 (79.55)	1.21 (0.63, 2.31)	154 (77.78)	1.29 (0.59, 2.80)
1	25 (24.75)	149 (33.48)	0.97 (0.46, 2.04)	68 (34.34)	0.93 (0.38, 2.25)
2	39 (38.61)	144 (32.36)	1.39 (0.68, 2.83)	59 (29.80)	1.64 (0.80, 3.84)
3	20 (19.80)	61 (13.71)	1.36 (0.59, 3.14)	27 (13.64)	1.41 (0.50, 3.96)
P-value for trend			0.26		0.21
Smokers					
0	51 (10.71)	66 (12.27)	Reference	25 (10.00)	Reference
≥1	425 (89.29)	472 (87.73)	0.69 (0.44, 1.08)	225 (90.00)	0.49 (0.27, 0.90)
1	150 (31.51)	182 (33.83)	0.62 (0.38, 1.01)	84 (33.60)	0.46 (0.24, 0.89)
2	168 (35.29)	171 (31.78)	0.79 (0.48, 1.29)	84 (33.60)	0.54 (0.28, 1.04)
3	107 (22.48)	119 (22.12)	0.69 (0.41, 1.16)	57 (22.80)	0.48 (0.24, 0.96)
P-value for trend			0.60		0.17

[1]Air pollution index was computed based on exposure to any source of household air pollution since adulthood, including solid fuels for cooking or heating and environmental tobacco smoking (yes = 1, no =0) and exposure to ambient air pollution (Tertile 1 = 0, Tertile 2 = 1, Tertile 3 = 2)[2]Models adjust for age, gender, education, race/ethnicity, drink-years, block group median household income in 1999 and packyears if applicable
[3]Controls originally matched to UADT cancers were used to assess the susceptibility of lung cancer

Table 4-20. Associations between air pollution index[1] and upper aerodigestive cancer susceptibility by smoking status

	Cases, N (%)	Combined controls, N (%)	Adjusted OR[2] (95% CI)	Lung controls[3], N (%)	Adjusted OR[2] (95% CI)
Nonsmokers					
0	24 (14.63)	91 (20.45)	Reference	47 (19.03)	Reference
≥1	140 (85.37)	354 (79.55)	1.67 (0.98, 2.85)	200 (80.97)	1.53 (0.85, 2.78)
1	49 (29.88)	149 (33.48)	1.54 (0.86, 2.78)	81 (32.79)	1.42 (0.74, 2.73)
2	54 (32.93)	144 (32.36)	1.54 (0.85, 2.79)	85 (34.41)	1.38 (0.71, 2.70)
3	37 (22.56)	61 (13.71)	2.39 (1.23, 4.66)	34 (13.77)	2.36 (1.10, 5.10)
P-value for trend			0.02		0.05
Smokers					
0	34 (8.48)	66 (12.27)	Reference	41 (14.24)	Reference
≥1	367 (91.52)	472 (87.73)	1.27 (0.78, 2.06)	247 (85.76)	1.53 (0.87, 2.67)
1	107 (26.68)	182 (33.83)	0.94 (0.56, 1.60)	98 (34.03)	1.10 (0.60, 2.04)
2	160 (39.90)	171 (31.78)	1.56 (0.92, 2.63)	87 (30.21)	1.89 (1.03, 3.49)
3	100 (24.94)	119 (22.12)	1.46 (0.84, 2.53)	62 (21.53)	1.82 (0.96, 3.48)
P-value for trend			0.02		< 0.01

[1]Air pollution index was computed based on exposure to any source of household air pollution since adulthood, including solid fuels for cooking or heating and environmental tobacco smoking (yes = 1, no =0) and exposure to ambient air pollution (Tertile 1 = 0, Tertile 2 = 1, Tertile 3 = 2)

[2]Models adjust for age, gender, education, race/ethnicity, drink-years, block group median household income in 1999 and packyears if applicable

[3]Controls originally matched to lung cancer were used to assess the susceptibility of UADT cancer

Table 4-21. Interactions between $PM_{2.5}$ concentration[1] one-year before diagnosis and smoking on lung cancer susceptibility

Smoking status	$PM_{2.5}$	Cases, N (%)	Combined controls, N (%)	Adjusted OR[2] (95% CI)	UADT controls[3], N (%)	Adjusted OR[2] (95% CI)
Non-smokers	Below median	37 (6.41)	223 (22.69)	Reference	102 (22.77)	Reference
Non-smokers	Above median	64 (11.09)	222 (22.58)	1.63 (1.02, 2.62)	96 (21.43)	1.64 (0.94, 2.86)
Smokers	Below median	221 (38.30)	263 (26.75)	4.54 (2.98, 6.92)	120 (26.79)	4.85 (2.90, 8.09)
Smokers	Above median	255 (44.19)	275 (27.98)	4.68 (3.05, 7.20)	130 (29.02)	5.01 (2.98, 8.43)
p-value for interaction				0.09		0.16

[1]$PM_{2.5}$ concentration among combined controls: below median ($\leq$ 19.1 $\mu g/m^3$) and above median (> 19.1 $\mu g/m^3$)

[2]Models adjust for age, gender, education, race/ethnicity, drink-years, block group median household income in 1999, and the household air pollution

[3]Controls originally matched to UADT cancers were used to assess the susceptibility of lung cancer

Table 4-22. Interactions between $PM_{2.5}$ concentration[1] one-year before diagnosis and smoking on UADT cancers susceptibility

Smoking status	$PM_{2.5}$	Cases, N (%)	Combined controls, N (%)	Adjusted OR[2] (95% CI)	UADT controls[3], N (%)	Adjusted OR[2] (95% CI)
Non-smokers	Below median	68 (12.04)	223 (22.69)	Reference	121 (22.62)	Reference
Non-smokers	Above median	96 (16.99)	222 (22.58)	1.36 (0.93, 2.00)	126 (23.55)	1.25 (0.81, 1.93)
Smokers	Below median	172 (30.44)	263 (26.75)	1.34 (0.93, 1.92)	143 (26.73)	1.33 (0.88, 2.01)
Smokers	Above median	229 (40.53)	275 (27.98)	1.70 (1.18, 2.46)	145 (27.10)	1.70 (1.12, 2.59)
p-value for interaction				0.78		0.94

[1]$PM_{2.5}$ concentration among combined controls: below median ($\leq$ 19.1 $\mu g/m^3$) and above median (> 19.1 $\mu g/m^3$)

[2]Models adjust for age, gender, education, race/ethnicity, drink-years, block group median household income in 1999, and the household air pollution

[3]Controls originally matched to lung cancer were used to assess the susceptibility of UADT cancers

Table 5-1. Summary of study methods and findings

Specific Aims	Aim 1	Aim 2	Aim 3
Outcomes	COVID-19		Lung and UADT cancers
	Incidence	Incidence and mortality	Susceptibility
Exposure	$PM_{2.5}$ and non-pharmacologic preventive initiatives	Vaccine coverage	$PM_{2.5}$, household air pollution, and both ambient and indoor air pollution
Sample size	3,096 counties	3,073 counties	577 lung cancer cases, 565 UADT cancers cases, and 983 controls
Source of population	The United States		Los Angeles county
Statistical methods	Negative binomial regression	Poisson with generalized linear models	Unconditional logistic regression
Evidence added	Long-term exposure $PM_{2.5}$ associated increase county-level COVID-19 incidence during the first two surges of COVID-19 pandemic in the US State-level facemasks mandates and stay home orders were effective	Associations between complete vaccination and booster and COVID-19 incidence and mortality during Alpha, Delta, and Omicron predominance	Associations of both ambient and household air pollution with lung and UADT susceptibility
Limitations	Ecologic fallacy, residual confounding, reliability on publicly available data		Overmatching, measurement error, low power in subgroup analyses

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