ESOPHAGUS

Long-Term Exposure to Fine Particulate Matter and Incidence of Esophageal Cancer: A Prospective Study of 0.5 Million Chinese Adults

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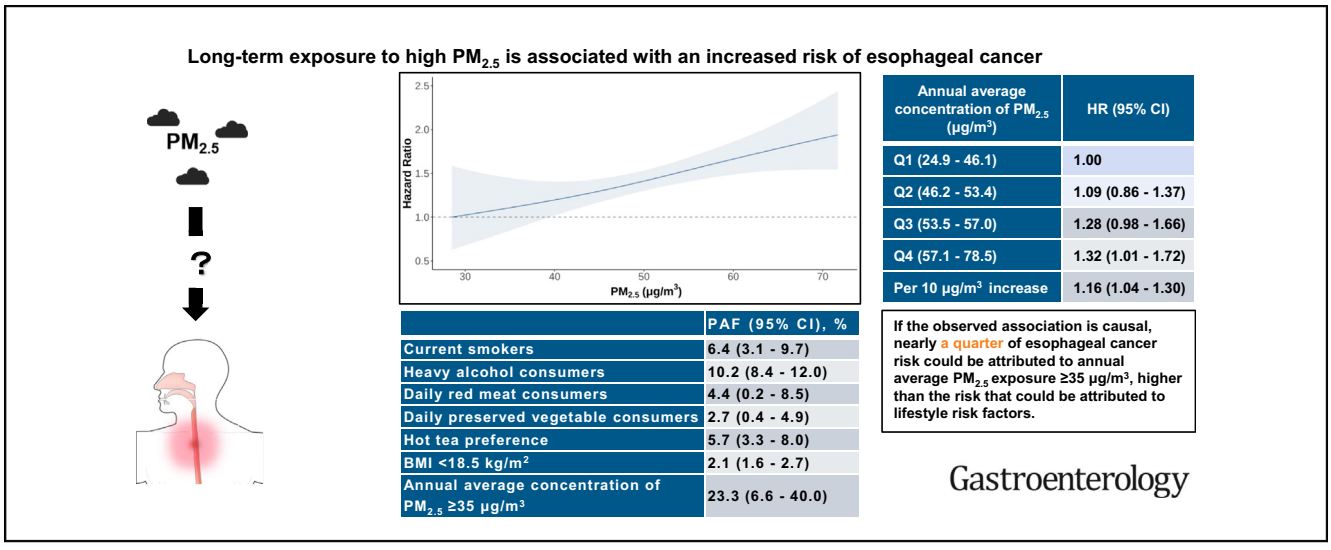

BACKGROUND & AIMS: Evidence is sparse and inconclusive on the association between long-term fine ($\leq$2.5 μm) particulate matter ($PM_{2.5}$) exposure and esophageal cancer. We aimed to assess the association of $PM_{2.5}$ with esophageal cancer risk and compared the esophageal cancer risk attributable to $PM_{2.5}$ exposure and other established risk factors. **METHODS:** This study included 510,125 participants without esophageal cancer at baseline from China Kadoorie Biobank. A high-resolution (1 $\times$ 1 km) satellite-based model was used to estimate $PM_{2.5}$ exposure during the study period. Hazard ratios (HR) and 95% CIs of $PM_{2.5}$ with esophageal cancer incidence were estimated using Cox proportional hazard model. Population attributable fractions for $PM_{2.5}$ and other established risk factors were estimated. **RESULTS:** There was a linear concentration–response relationship between long-term $PM_{2.5}$ exposure and esophageal cancer. For each 10-$\mu g/m^3$ increase in $PM_{2.5}$, the HR was 1.16 (95% CI, 1.04–1.30) for esophageal cancer incidence. Compared with the first quarter of $PM_{2.5}$ exposure, participants in the highest quarter had a 1.32-fold higher risk for esophageal cancer, with an HR of 1.32 (95% CI, 1.01–1.72). The population attributable risk because of annual average $PM_{2.5}$ concentration $\geq$35 $\mu g/m^3$ was 23.3% (95% CI, 6.6%–40.0%), higher than the risks attributable to lifestyle risk factors. **CONCLUSIONS:** This large prospective cohort study of Chinese adults found that long-term exposure to $PM_{2.5}$ was associated with an elevated risk of esophageal cancer. With stringent air pollution

mitigation measures in China, a large reduction in the esophageal cancer disease burden can be expected.

Keywords: Ambient Air Pollution; Digestive Tract; Malignant Tumor; Observational Study.

ESOPHAGUS

Esophageal cancer is one of the most common cancers worldwide, with an estimated 535,000 new cases and 498,000 deaths contributing to 2.24% and 4.98% of new cancer cases and deaths in 2019, respectively.[1] China has a heavy esophageal cancer burden, accounting for approximately one-half of new cases and deaths from esophageal cancer globally.[2] The well-established risk factors for esophageal cancer include smoking, alcohol consumption, low consumption of fruits and vegetables, high consumption of preserved vegetables and red meat, hot food and beverage consumption, and unhealthy weight.[2–6] However, these risk factors cannot explain all mortality and morbidity, and efforts to investigate unknown risk factors are still in progress.

China is one of the most fine ($\leq$2.5 μm) particulate matter ($PM_{2.5}$)–polluted countries, with a large proportion of the population exposed to an annual average of $PM_{2.5}$ above the World Health Organization's[7] highest interim target guideline of 35 $\mu g/m^3$. Outdoor air pollution and PM were classified as Group 1 human carcinogens for lung cancer by the International Agency for Research on Cancer.[8] Long-term $PM_{2.5}$ exposure can induce chronic low-grade inflammation and oxidative stress at the local and systemic levels and further trigger changes of genetic material, which may relate to the increased risk of lung cancer and non-lung cancer.[7]

Long-term $PM_{2.5}$ exposure is a well-established risk factor for lung cancer,[7,9,10] but the evidence is sparse and inconclusive on the association between $PM_{2.5}$ and esophageal cancer. Four cohort studies investigated the associations of long-term $PM_{2.5}$ exposure with gastrointestinal or upper digestive tract cancers (including esophageal cancer), yielding mixed results of positive[11,12] and null associations.[13,14] Two previous nationwide ecological studies from China found that long-term $PM_{2.5}$ exposure was associated with an increased risk of esophageal cancer.[15,16] However, another ecological study from the United States with low $PM_{2.5}$ levels did not find associations between $PM_{2.5}$ and most non-lung cancers, including esophageal cancer.[17] Ecological studies can only provide clues about causal relationships due to possible ecological fallacies and difficulties in controlling confounders at the individual level. Only 2 US cohort studies have specifically explored the association between long-term $PM_{2.5}$ exposure and esophageal cancer mortality, predominantly adenocarcinoma,[18] and found an inverse or null association.[19,20] There is still a lack of high-quality evidence on the association between $PM_{2.5}$ exposure and esophageal cancer in China, with high $PM_{2.5}$ exposure and esophageal squamous cell carcinoma (ESCC) being the predominant histologic type.[18]

WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

Outdoor air pollution and particulate matter were classified as Group 1 human carcinogens for lung cancer. However, whether there is an association between long-term exposure to $PM_{2.5}$ and esophageal cancer risk remains unclear.

NEW FINDINGS

There was a linear relationship between fine ($\leq$2.5 μm) particulate matter ($PM_{2.5}$) exposure and esophageal cancer risk. If the observed association is causal, nearly one-quarter of esophageal cancer risk could be attributed to annual average $PM_{2.5}$ exposure $\geq$35 $\mu g/m^3$.

LIMITATIONS

$PM_{2.5}$ exposures were assigned to participants according to their nearby clinics, possibly leading to nondifferential misclassification and underestimation of the association.

CLINICAL RESEARCH RELEVANCE

Our findings indicate that the disease burden of esophageal cancer may be reduced by implementing stricter air pollution control policies in China.

BASIC RESEARCH RELEVANCE

Long-term exposure to $PM_{2.5}$ was associated with esophageal cancer risk. Future studies are warranted to explore the mechanism behind the association.

Based on 0.5 million Chinese adults from China Kadoorie Biobank, we aimed to investigate the association of $PM_{2.5}$ exposure with esophageal cancer incidence. When the associations were observed, we further compared esophageal cancer risk attributable to $PM_{2.5}$ exposure and other established risk factors.

Methods

Population

Details of the China Kadoorie Biobank cohort have been described elsewhere.[21] Briefly, the baseline survey was conducted between 2004 and 2008. A total of 512,725 participants aged 30–79 years and living within 1 km of the study clinics were enrolled from 10 predetermined regions, including 5 urban (Harbin, Qingdao, Suzhou, Liuzhou, and Haikou) and 5 rural (Gansu, Henan, Sichuan, Zhejiang, and Hunan) areas in China. Trained interviewers collected baseline information for participants using laptop-based questionnaires with built-in quality-control procedures, which can prompt and correct errors during data collection and entry. Participants also completed

Abbreviations used in this paper: **BMI, body mass index; ESCC, esophageal squamous cell carcinoma; HR, hazard ratio; $PM_{2.5}$, fine (≤2.5 μm) particulate matter.**

Most current article

0016-5085
https://doi.org/10.1053/j.gastro.2023.03.233

physical measurements and provided blood samples. All participants provided written informed consent before data collection. The study was approved by the Ethical Review Committee of the Chinese Center for Disease Control and Prevention (Beijing, China) and the Oxford Tropical Research Ethics Committee, University of Oxford (Oxford, United Kingdom).

In the current study, we excluded participants who reported a history of cancer at baseline (n = 2578) or those without body mass index (BMI) data (n = 2). There was no missing value in other variables included in our analyses. As the $PM_{2.5}$ data were available between 2005 and 2017, we further excluded participants who completed the baseline survey in 2004 and had incident cancer documented before January 1, 2005 (n = 23), leaving 510,125 participants for analysis. A flow diagram of the study population is provided in Supplementary Figure 1.

Assessment of Fine ($\leq$2.5 μm) Particulate Matter

Daily $PM_{2.5}$ concentrations at 1 × 1 km spatial resolution from 2005 to 2017 were estimated using a satellite-based model, of which details have been published elsewhere.[22,23] Briefly, a random forest algorithm was implemented to estimate daily $PM_{2.5}$ concentrations. The model was trained using $PM_{2.5}$ measurements from over 1300 ground monitoring in 2013–2017 as the dependent variable, and using Multi-Angle Implementation of Atmospheric Correction aerosol optical depth values as the main independent variable. Other predictors included meteorological parameters, land use, population density, and the Modern-Era Retrospective Analysis for Research and Applications $PM_{2.5}$ products. A gap-filling approach was implemented to address the issue of missing aerosol optical depth values. Estimated $PM_{2.5}$ values were yielded by combining results from models built with or without aerosol optical depth values. Our $PM_{2.5}$ estimates were highly consistent with out-of-sample $PM_{2.5}$ measurements, with a cross-validation R^2 of 0.84 at the daily level. For temporal variations, we conducted an external validation by comparing $PM_{2.5}$ measurements during 2008–2012 from provincial monitoring stations that were not included in model development with their corresponding predictions generated by our random forest models.[24] The results showed good consistency between the measurements and predictions, with an R^2 of 0.70 and a root mean square error of 20.92 $\mu g/m^3$, indicating that our model has good performance in capturing the temporal variations of historical data. Historical $PM_{2.5}$ data in 2005–2012 were derived based on this model.

Annual average $PM_{2.5}$ concentrations were assigned to each participant by linking the values of the 1 × 1 km grid to the geocodes of the study clinics in which they were recruited. We used annual average $PM_{2.5}$ concentrations as a time-varying variable in the primary analyses to account for the temporal variation of $PM_{2.5}$ in the study period (detailed in the Supplementary Methods and Supplementary Tables 1 and 2).

Assessment of Covariates

The baseline questionnaires collected sociodemographic characteristics, lifestyle factors, passive smoking, household air pollution from solid fuel use, self-rated health, and family history of cancer. Sociodemographic characteristics were age, sex, education, household income, and occupation. Lifestyle factors included tobacco smoking, alcohol consumption, consumption of red meat, fresh fruits, and fresh and preserved vegetables, consumption of tea and hot tea preference, physical activity, and sedentary leisure time. Information on passive smoking included hours of second-hand smoke exposure per week and years of living with a smoker. We collected fuel types for cooking and heating and cookstove ventilation at participants' baseline residence and up to 2 previous residences. Detailed definitions and categorizations of covariates were provided in Supplementary Methods.

Height, weight, waist circumference, and hip circumference were measured by trained staff using calibrated instruments. BMI was calculated as weight (kg) divided by the square of standing height (m), and waist-to-hip ratio as the ratio of waist circumference (cm) to hip circumference (cm).

Ascertainment of Outcomes

Diseases, hospitalization events, and deaths occurred during the follow-up were obtained by linking to the national health insurance database and local disease and death registry systems. We performed annual active follow-up to collect the disease status and vital information for those who failed to link to the national health insurance database. Those who moved away from the city were regarded as lost to follow-up, and that proportion was <1% until December 31, 2017. Causes of death were mainly ascertained through official death certificates and supplemented by checking hospital records or a verbal autopsy using a validated instrument. All events were coded according to the International Classification of Diseases, 10th Revision.[25] The primary outcome in this study was esophageal cancer, coded as C15. We also used a negative control outcome, that is, injuries to upper extremities (International Classification of Diseases, 10th Revision codes S40-S69), to detect uncontrolled confounding.

During the follow-up, medical records of incident cases were retrieved and adjudicated by trained staff to verify disease diagnosis. Adjudication of incident cancer cases is ongoing. In the current study population, medical records of 1212 incident esophageal cancer cases were retrieved and adjudicated, and 1179 (97.3%) of them were confirmed as esophageal cancer. Pathology reports with clear diagnoses were retrieved for 778 esophageal cancer cases, and 721 (92.7%) of them were ESCC.

Statistical Analysis

Baseline characteristics were presented for all participants and 2 groups according to the median of average $PM_{2.5}$ concentrations from 2005 to 2017 as means (for continuous variables) or numbers and percentages (for categorical variables), with adjustment for age, sex, and study areas. Person-years of follow-up were calculated from January 1, 2005 or the date of enrollment, whichever came last, to the date of esophageal cancer diagnosis, death, loss to follow-up, or December 31, 2017, whichever came first.

Cox proportional hazard models were implemented to estimate the hazard ratio (HR) and 95% CI of long-term $PM_{2.5}$ exposure with esophageal cancer incidence, with annual average $PM_{2.5}$ concentrations included as a time-varying variable (in 1-year scale) and the follow-up time as the underlying

time scale. The models were stratified by 5-year age groups and study areas. We used Schoenfeld residuals to test the proportional hazard assumption, and no violation was observed. Potential confounders were adjusted for in the models, including age, sex, education, household income, occupation, tobacco smoking, alcohol consumption, consumption of red meat, fresh fruits, fresh vegetables, and preserved vegetables, consumption of tea and hot tea preference, total physical activity levels, sedentary leisure time, fuel types for cooking and heating at baseline residence, duration of solid fuel use at the past 3 residences, cookstove ventilation at baseline residence, exposure to second-hand smoke, duration of living with a smoker, BMI, waist-to-hip ratio, self-rated health status, and family history of cancer.

We used penalized spline to assess the concentration–response relationship between $PM_{2.5}$ and esophageal cancer incidence.[26] After confirming the linear relationship, we separately estimated HRs of each 10-$\mu g/m^3$ increase in $PM_{2.5}$ and the 4 quartile groups of $PM_{2.5}$ with esophageal cancer incidence. Linear trends were tested by assigning the median value of each quartile group and treating that variable as continuous in the models.

We conducted several sensitivity analyses by including the $PM_{2.5}$ as a continuous variable, including extending the exposure time window by using 3-year or 5-year average $PM_{2.5}$ concentrations as the time-varying variable, or using average $PM_{2.5}$ concentrations from 2005 to 2017 as a time-invariant variable referring to previous studies[9,26]; excluding participants with incident esophageal cancer in the first year or in the first 3 years; adding a random intercept for study clinics, or adding nested random intercepts for study areas and study clinics to account for clustering and unmeasured confounder within communities and study areas[27]; excluding participants from Henan, an area in China with a high incidence of esophageal cancer, with the most esophageal cancer cases and the highest average $PM_{2.5}$ concentration among 10 study areas; using age as the time scale; and only considering ESCC cases confirmed by pathology reports as occurrence of the study outcome.

We performed subgroup analysis according to age, sex, urban or rural areas, alcohol consumption, tobacco smoking, second-hand smoking exposure, and household cooking and heating pollution from solid fuel use. The heterogeneity of associations between subgroups was tested using Cochrane's Q test.

We calculated the population attributable fraction for $PM_{2.5}$ and 8 other risk factors for esophageal cancer, including current smokers, heavy alcohol consumers, daily red meat consumers, not daily fresh fruits consumers, not daily fresh vegetable consumers, daily preserved vegetable consumers, daily tea consumers with a preference for hot or burning hot tea, and low BMI, using a method adapted from the Global Burden of Disease Study 2019[28] (detailed in Supplementary Methods). Adjusted HR for each risk factor was estimated by treating $PM_{2.5}$ and BMI as continuous variables and the other 7 risk factors as binary variables in the Cox proportional hazard model, with adjustment for the other covariates. The highest interim target of annual average concentration <35 $\mu g/m^3$ in World Health Organization's guideline[29] was used as the reference level for $PM_{2.5}$ and 18.5 kg/m^2 for BMI. The distribution of risk factors was obtained in the study population. The CI was generated using the delta method.

Statistical significance was set at $P < .05$ with 2-sided test. All statistical analyses were performed using Stata, version 17.0 (StataCorp) and R, version 4.0.3 (R Foundation for Statistical Computing).

Role of the Funding Source

The funders had no role in the study design, data collection, data analysis and interpretation, writing of the report, or the decision to submit the article for publication.

Results

The mean ± SD $PM_{2.5}$ concentration from 2005 to 2017 among 10 study areas was 52.27 ± 10.63 $\mu g/m^3$, ranging from 26.32 ± 0.35 $\mu g/m^3$ in Haikou to 70.89 ± 1.41 $\mu g/m^3$ in Henan. In most study areas, the annual average $PM_{2.5}$ concentrations showed a slight upward trend from 2005 to 2013 and a downward trend after 2013 (Supplementary Figure 2). Mean ± (SD) age of the eligible participants (n = 510,125) was 52.0 ± 10.7 years; 59.0% were women and 44.1% lived in urban areas. Participants exposed to a high level of $PM_{2.5}$ (above the median) were more likely to live in urban areas (Table 1).

Distributions of cohort entry year and years of follow-up are presented in Supplementary Figure 3. During a median follow-up of 11.12 years (5,517,479 person-years), we documented 2550 incident cases of esophageal cancer and 4849 cases of injuries to upper extremities. After adjusting for potential risk factors for esophageal cancer, there was a linear relationship between long-term $PM_{2.5}$ exposure and esophageal cancer incidence (P for a nonlinear trend = .669) (Figure 1). With each 10-$\mu g/m^3$ increase in $PM_{2.5}$, the HR for esophageal cancer incidence was 1.16 (95% CI, 1.04–1.30) (Table 2). Using the lowest group of $PM_{2.5}$ exposure as the reference, the HRs for the other 3 quartile groups, from low to high, were 1.09 (95% CI, 0.86–1.37), 1.28 (95% CI, 0.98–1.66), and 1.32 (95% CI, 1.01–1.72) (P for trend = .033). After adjusting for the same covariates, we observed a statistically insignificant association of each 10-$\mu g/m^3$ increase in $PM_{2.5}$ with injuries to upper extremities, with an HR of 1.03 (95% CI, 0.97–1.09; $P = .950$).

There was no statistically significant difference in the associations of $PM_{2.5}$ exposure with esophageal cancer incidence among various subpopulations defined by age, sex, alcohol consumption, smoking status, second-hand smoke exposure, and indoor heating pollution (Figure 2). The associations were stronger among rural compared with urban residents (P for heterogeneity $< .001$), and among participants cooking with solid fuels but without cookstove ventilation (P for heterogeneity = .005).

Sensitivity analyses showed the robustness of our results (Supplementary Table 3). When using 3-year or 5-year average $PM_{2.5}$ as the time-varying variable, or using average $PM_{2.5}$ concentrations from 2005 to 2017 as long-term $PM_{2.5}$ exposure, the association estimates of $PM_{2.5}$ with esophageal cancer incidence increased. The exclusion of esophageal cancer cases that occurred within the first year of follow-up did not alter the results substantially. After further excluding new cases within the first 3 years of follow-up, the

Table 1. Baseline Characteristics of Participants by Median of Average $PM_{2.5}$ Concentration From 2005 to 2017

Characteristic	Total population	Annual average concentration of $PM_{2.5}$	
		<53.5 $\mu g/m^3$	≥53.5 $\mu g/m^3$
Participants, n	510,125	259,158	250,967
Sex, female, n (%)	300,900 (59.0)	155,597 (60.0)	145,303 (57.9)
Study area, urban, n (%)	224,764 (44.1)	89,223 (34.4)	135,541 (54.0)
Age, *y*, mean ± SD	52.0 ± 10.7	52.1 ± 10.8	51.8 ± 10.5
Education, middle school or higher, n (%)	251,135 (49.2)	116,196 (47.9)	134,939 (50.7)
Household income ≥20,000 RMB/y, n (%)	217,970 (42.7)	93,246 (40.5)	124,724 (44.9)
Married status, married, n (%)	462,202 (90.6)	232,918 (90.6)	229,284 (90.6)
Smoking status, current smoker,[a] n (%)	150,081 (29.4)	74,630 (29.7)	75,451 (29.2)
Heavy alcohol consumer,[b] n (%)	55,203 (10.8)	24,407 (10.0)	30,796 (11.5)
Daily consumer of, n (%)			
Red meat	149,193 (29.2)	76,950 (26.7)	72,243 (32.0)
Fresh fruits	95,877 (18.8)	35,595 (17.6)	60,282 (19.7)
Fresh vegetables	483,441 (94.8)	236,417 (94.3)	247,024 (96.2)
Preserved vegetables	80,542 (15.8)	15,908 (13.0)	64,634 (16.9)
Tea with a preference for hot or burning-hot tea	81,427 (16.0)	42,182 (15.1)	39,245 (17.1)
Total physical activity, *MET-h/d*	21.1	22.4	19.8
Leisure sedentary time, *h/wk*	21.1	20.9	21.3
BMI, kg/m^2	23.7	23.6	23.8
Waist-to-hip ratio	0.882	0.879	0.884
Cooking with solid fuels at baseline residence, n (%)	174,397 (34.2)	105,875 (35.6)	68,522 (32.4)
Heating with solid fuels at baseline residence, n (%)	186,863 (36.6)	110,099 (41.0)	76,764 (32.7)
Having cookstove ventilation at baseline residence, n (%)	268,073 (52.6)	133,794 (54.1)	134,279 (50.6)
Self-rated good health, n (%)	234,040 (45.9)	105,441 (46.0)	128,599 (45.8)
Family history of cancer, n (%)	85,662 (16.8)	29,350 (16.4)	56,312 (17.1)
Annual concentration of $PM_{2.5}$, $\mu g/m^3$, mean ± SD	52.3 ± 10.6	44.8 ± 8.3	59.9 ± 6.5

NOTE. All percentages and means in 2 $PM_{2.5}$ groups were adjusted for age, sex, and study area, except for these 3 variables. All *P* values for difference between 2 $PM_{2.5}$ groups were <.001, except for married status ($P = .750$), smoking status ($P = .003$), self-rated good health ($P = .352$), and family history of cancer ($P = .001$).
MET, metabolic equivalent of task; RMB, Chinese renminbi.
[a]Former smokers who have stopped smoking because of illness were included.
[b]Heavy alcohol consumer refers to participants with a pure alcohol consumption ≥30 g/d or former weekly drinkers.

HR estimate was slightly attenuated. Other sensitivity analyses, including the exclusion of participants in Henan, the addition of a random intercept for study clinics or nested random intercepts for study areas and study clinics, or the use of age as a time scale, also did not alter our results. When only considering ESCC cases confirmed by pathology reports as occurrence of the study outcome, the estimate of association increased slightly.

For all participants, the population attributable risk because of annual average $PM_{2.5}$ concentration ≥35 $\mu g/m^3$ was 23.3% (95% CI, 6.6%–40.0%), suggesting that approximately one-quarter of the incident esophageal cancer cases in this population during the follow-up period might have been prevented if all participants were exposed to $PM_{2.5}$ <35 $\mu g/m^3$ (Table 3). The incident esophageal cancer cases were also attributed to, in order of population attributable fraction, heavy alcohol consumption, current smoking, hot tea preference, daily red meat consumption, daily preserved vegetable consumption, and BMI < 18.5 kg/m^2.

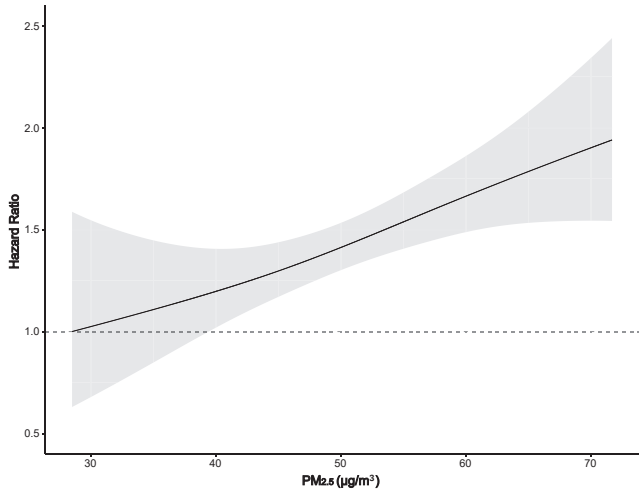

Figure 1. Concentration–response relationship between long-term $PM_{2.5}$ exposure and esophageal cancer incidence. The curve was observed to be linear, with the *P* for a nonlinear trend of .669. The adjusted covariates were consistent with those in the models of Table 2. *Solid line* represents HRs and the *gray ribbon* represents the 95% CI.

Discussion

In this large prospective cohort study of Chinese adults, we observed linear concentration–response relationships between long-term $PM_{2.5}$ exposure and esophageal cancer incidence. The associations with esophageal cancer incidence were greater among rural residents and participants cooking with solid fuels but without ventilation than their counterparts. We estimated that nearly one-quarter of esophageal cancer risk could be attributed to annual average $PM_{2.5}$ exposure $\geq$35 $\mu g/m^3$, which was higher than the risks that could be attributed to lifestyle risk factors, such as heavy alcohol consumption or current smoking.

There are few cohort studies on the association between $PM_{2.5}$ and esophageal cancer risk, with only 2 studies conducted in the US population. In an analysis of Cancer Prevention Study-II cohort data, 623,048 participants 30 years and older were followed-up for 19.2 years and documented 1180 esophageal cancer deaths. No statistically significant association between $PM_{2.5}$ and esophageal cancer mortality was observed (HR, 1.02; 95% CI, 0.93–1.13).[20] Another US study, including 635,539 participants aged 18–84 years, identified 599 esophageal cancer deaths during follow-up and found an inverse association between $PM_{2.5}$ and esophageal cancer mortality (HR, 0.59; 95% CI, 0.38–0.90).[19] Unlike the findings of these 2 studies, we found a linear concentration–response relationship between $PM_{2.5}$ and esophageal cancer risk in the current Chinese population. This difference may be due to the low $PM_{2.5}$ levels in 2 US studies, with mean values of 12.6 and 10.7 $\mu g/m^3$. In addition, there is a difference in the predominant histologic subtype of esophageal cancer between Chinese and US populations, namely, ESCC and adenocarcinoma, respectively.[18]

Two recent ecological studies from China, covering 213 county-level cities and a population of more than 320 million, found positive associations between $PM_{2.5}$ and incidence of esophageal cancer between the mid-2000s and 2015.[15,16] In these 2 studies, the association became stronger with the exposure time window extended. Our study findings were similar. When the exposure time

Table 2. Associations of Esophageal Cancer Incidence With Long-Term $PM_{2.5}$ Exposure

Annual average concentration of $PM_{2.5}$, $\mu g/m^3$	Case	Incident rate (per 100,000 PYs)	HR (95% CI)	*P* for trend
Q1 (24.9–46.1)	254	18.74	Ref	.033
Q2 (46.2–53.4)	364	26.49	1.09 (0.86–1.37)	—
Q3 (53.5–57.0)	413	29.23	1.28 (0.98–1.66)	—
Q4 (57.1–78.5)	1,519	110.47	1.32 (1.01–1.72)	—
Per 10-$\mu g/m^3$ increase	2,550	46.22	1.16 (1.04–1.30)	—

NOTE. The models were adjusted for age (years), sex, education (no formal school, primary school, middle school, or high school or above), household income (<10,000, 10,000–19,999, or ≥20,000 Chinese renminbi/y), occupation (famers, factory workers, administrators or managers, technical workers, sales or service workers, self-employed, or others), tobacco smoking (never smokers, smoking quitters because of reasons other than illness, quitters because of illness or current smokers: 1–14, 15–24, or ≥25 cigarettes or equivalent per day), alcohol consumption (never regular or less than weekly drinkers, former weekly drinkers, weekly but not daily drinkers, daily drinkers: <30, 30–59, or ≥60 g/d of pure alcohol), consumption of red meat, fresh fruits, fresh vegetables, and preserved vegetables (days per week; assigning according to the midpoint of each frequency category), consumption of tea and hot tea preference (less than daily drinkers, daily drinkers and preferring: warm tea, hot tea, or burning-hot tea), total physical activity levels (metabolic equivalent of task h/d), leisure sedentary time (h/d), fuel types for cooking and heating at baseline residence (clean fuels, solid fuels, or other fuels or no monthly cooking or heating in the winter), duration of solid fuel use at the past 3 residences (years), cookstove ventilation at baseline residence (yes or no), hours of exposure to second-hand smoke (h/d), duration of living with a smoker (years), BMI (kg/m^2), waist-to-hip ratio, self-rated health status (excellent, good, fair, or poor), and family history of cancer (yes or no).
PY, person-year; Q, quartile.

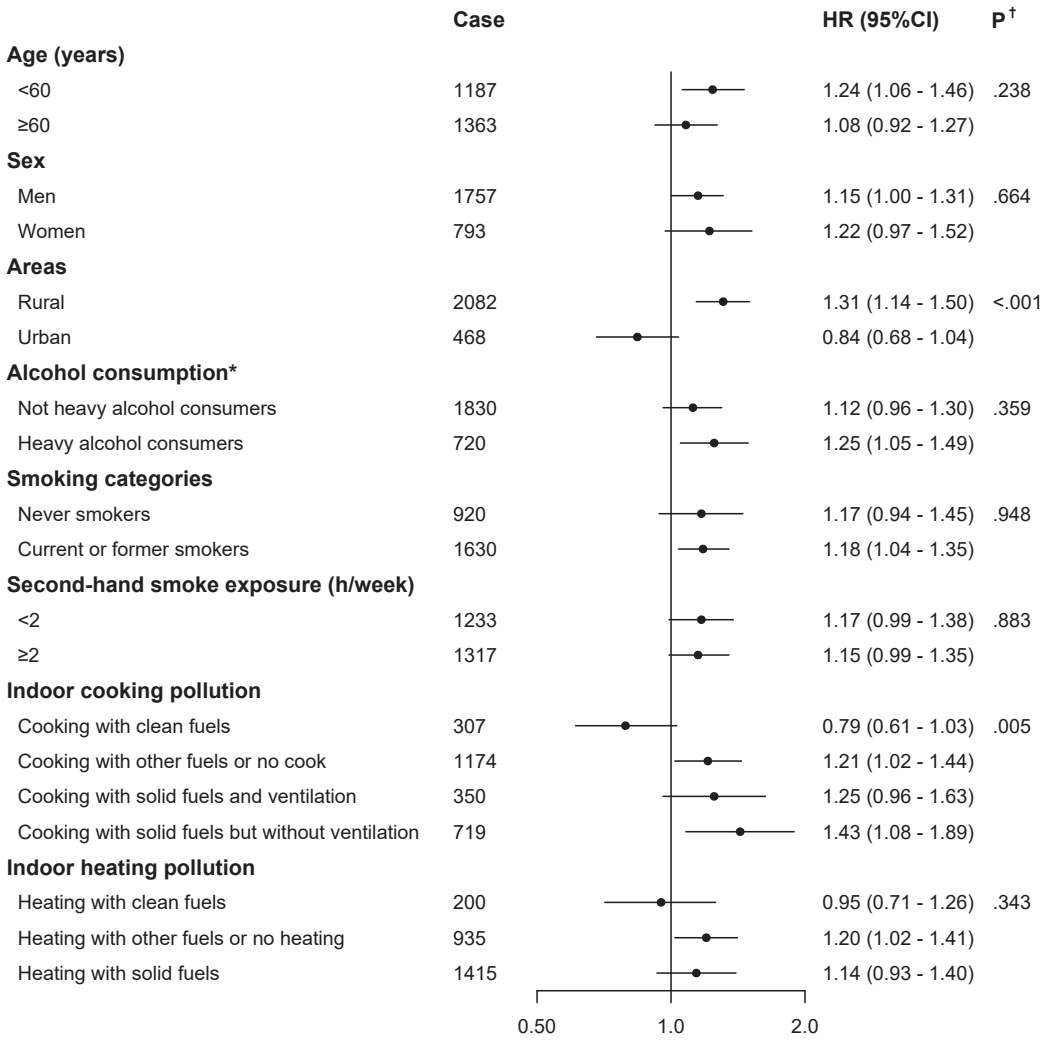

Figure 2. Subgroup analyses of associations between long-term $PM_{2.5}$ exposure and esophageal cancer incidence according to baseline characteristics. The HRs and 95% CIs were for the association of esophageal cancer incidence with per 10-μg/m^3 increase in $PM_{2.5}$. The adjusted covariates were consistent with those in the models of Table 2, except for the subgroup characteristics. *Heavy alcohol consumers refer to participants with a pure alcohol consumption ≥30 g/d or former weekly drinkers. †*P* values for heterogeneity between subgroups were obtained from Cochrane's *Q* test.

window was extended from 1 year to 3–5 years or the total study period, the association estimates increased, suggesting a possible cumulative effect of the $PM_{2.5}$ exposure on esophageal cancer.

In the present study, the association estimates between $PM_{2.5}$ and esophageal cancer risk were greater among rural residents. The above-mentioned ecological study in China had similar findings.[16] The possible reasons for the urban–rural difference are that the prevalence of traditional risk factors and the source and components of $PM_{2.5}$ differ between urban and rural areas.[30–32] Our study also found that the association between $PM_{2.5}$ exposure and esophageal cancer risk was stronger in participants cooking with solid fuels but without ventilation. Solid fuel combustion can produce particulate matter and other carcinogens.[33,34] Our results suggest that indoor air pollution from cooking and ambient $PM_{2.5}$ exposure may have a synergistic effect on esophageal cancer risk.

The association between $PM_{2.5}$ exposure and esophageal cancer risk is plausible. Inflammation and oxidative damage caused by $PM_{2.5}$ further lead to DNA damage, gene mutations, and epigenetic modifications.[7,35] $PM_{2.5}$-bound polycyclic aromatic hydrocarbon and heavy metal may also accelerate this process.[36–38] High $PM_{2.5}$ exposure was associated with increased methylation of the DLEC1 gene in a study of 496 Chinese participants.[39] The excessive methylation of the DLEC1 gene, a tumor suppressor gene, has been associated with elevated ESCC risk.[40] Further research is needed to elucidate the mechanism underlying the carcinogenesis of $PM_{2.5}$ related to non-lung cancer.

Compared with association metrics (eg, HR), population attributable fraction can provide more information on public health significance. If the association between $PM_{2.5}$ and esophageal cancer was causal, we estimated that approximately one-quarter of incident cases in our population during follow-up would be avoided by reducing

Table 3. Population Attributable Fractions for $PM_{2.5}$ and Other Risk Factors for Esophageal Cancer Incidence

Variable	Prevalence, %	HR (95% CI)[a]	PAF (95% CI), %
Current smoker[b]	28.9	1.24 (1.11–1.37)	6.4 (3.1–9.7)
Heavy alcohol consumer[c]	10.5	2.08 (1.88–2.30)	10.2 (8.4–12.0)
Daily red meat consumer	29.5	1.15 (1.01–1.32)	4.4 (0.2–8.5)
Not daily fresh vegetable consumer	5.1	1.05 (0.83–1.34)	NA[d]
Not daily fresh fruit consumer	81.1	1.13 (0.95–1.35)	NA[d]
Daily preserved vegetable consumer	16.0	1.17 (1.03–1.33)	2.7 (0.4–4.9)
Hot tea preference	15.8	1.38 (1.22–1.56)	5.7 (3.3–8.0)
BMI <18.5 kg/m^2	4.1	1.07 (1.06–1.09)	2.1 (1.6–2.7)
Annual average concentration of $PM_{2.5}$ ≥ 35 μg/m^3	94.5	1.15 (1.03–1.29)	23.3 (6.6–40.0)

NOTE. When calculating PAF, the $PM_{2.5}$ and BMI were treated as continuous variables, and the other 7 risk factors were treated as binary variables. The adjusted covariates were consistent with those in the models of Table 2, except for these 9 risk factors.
PAF, population attributable fraction.
[a]HRs and 95% CIs for binary risk factors, each 1-kg/m^2 decrease in BMI and each 10-μg/m^3 increase in $PM_{2.5}$ were shown.
[b]Former smokers who have stopped smoking because of illness were included.
[c]Heavy alcohol consumer refers to participants with a pure alcohol consumption $\geq$30 g/d or former weekly drinkers.
[d]PAFs for not daily fresh vegetable and fruit consumer were not estimated, as the nonstatistically significant associations of them with esophageal cancer in the current study.

annual average $PM_{2.5}$ exposure lower than the World Health Organization's highest interim target guideline of 35 μg/m^3. This proportion was higher than that which can be prevented by adherence to healthy lifestyle, such as not drinking heavily or not smoking.

This is the first cohort study to identify the association between long-term $PM_{2.5}$ exposure and esophageal cancer risk in China, the country with the heaviest burden of esophageal cancer and high levels of air pollution. Our study has some strengths. First, the large sample size, long follow-up period, and large number of esophageal cancer cases and deaths powered the study to detect the associations of interest in the whole population and across important subgroups. Second, the exposure assessment model with high spatiotemporal resolution enabled $PM_{2.5}$ prediction over the entire study period, thus allowing us to account for the spatiotemporal variation of $PM_{2.5}$ in the analyses. Third, we compared the esophageal cancer risk attributable to $PM_{2.5}$ and other well-established risk factors in the same study population, providing an intuitive impression of the hazards of $PM_{2.5}$ on esophageal cancer risk.

Our study also has several limitations. First, we did not analyze ESCC and esophageal adenocarcinoma separately because the information on histologic subtype was unavailable for all esophageal cancer cases in this study. However, $>$91% of esophageal cancer in China are ESCC,[18] similar to the findings in our case adjudication. When we considered ESCC cases only in the sensitivity analysis, the association estimates increased. Second, despite the high spatiotemporal resolution of our satellite model, $PM_{2.5}$ exposures were assigned to individuals according to their nearby clinics, possibly resulting in exposure misclassification. However, this misclassification was more likely to be non-differential and lead to an underestimation of the association. Third, we did not consider participants' home address change in our analyses, which may also bring about exposure misclassification. However, $<$1% of participants moved out of their baseline cities by the end of 2017 and were considered lost to follow-up. Approximately 1% of participants moved out of their baseline administrative units, but remained within the study areas. Such a small proportion of intra-area movement should only have a minor impact on the results. Fourth, we were unable to consider other pollutants and $PM_{2.5}$ components due to lack of information. Future advancements in exposure modeling and/or air pollution products are warranted to fill this gap. Finally, given that our participants were exposed to relatively higher $PM_{2.5}$ levels, our findings should be extrapolated cautiously to populations exposed to other levels.

Our study provides important epidemiological evidence that long-term $PM_{2.5}$ exposure is an independent risk factor for esophageal cancer, especially ESCC. Our findings extend the existing understanding of the potentially harmful effects of $PM_{2.5}$ on non-lung cancer. With stringent air pollution mitigation measures in China, a large reduction in the esophageal cancer disease burden can be expected.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2023.03.233.

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Received October 20, 2022. Accepted March 2, 2023.

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Acknowledgments
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Most importantly, the authors acknowledge the participants in the study and the members of the survey teams in each of the 10 regional centers, as well as the project development and management teams based at Beijing, Oxford, and the 10 regional centers.
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Conflicts of interest
The authors disclose no conflicts.

Funding
This work was supported by National Natural Science Foundation of China (82192904, 82192901, 82192900, 82103790, and 92043301). The China Kadoorie Biobank baseline survey and the first re-survey were supported by a grant from the Kadoorie Charitable Foundation in Hong Kong. Long-term follow-up is supported by grants from the UK Wellcome Trust (212946/Z/18/Z, 202922/Z/16/Z, 104085/Z/14/Z, and 088158/Z/09/Z), grants from the National Key R&D Program of China (2016YFC0900500), National Natural Science Foundation of China (91846303, 91843302, 81390540 and 81941018), and Chinese Ministry of Science and Technology (2011BAI09B01). The funders had no role in the study design, data collection, data analysis and interpretation, writing of the report, or the decision to submit the article for publication.

Data Availability
Study protocol, cohort description, and questionnaires are available at https://www.ckbiobank.org/; statistical code is available from Dr. Lv (e-mail: lvjun@bjmu.edu.cn); and data access policy and procedures are available at the study website (www.ckbiobank.org).

Supplementary Methods

Definitions and Categorizations of Covariates

Sociodemographic characteristics included age, sex, education, household income, and occupation. Education was categorized as no formal school, primary school, middle school, or high school or above. Household income was classified as annual income <10,000, 10,000–19,999, or ≥20,000 Chinese renminbi. Occupation was categorized as farmers, factory workers, administrators or managers, technical workers, sales or service workers, self-employed, or others.

Lifestyle factors were tobacco smoking; alcohol consumption; consumption of red meat, fresh fruits, and fresh and preserved vegetables; consumption of tea and hot tea preference; physical activity; and sedentary leisure time. For tobacco smoking, we asked ever smokers about frequency, type, and amount of tobacco smoked per day, and asked former smokers about years since quitting and the reason for quitting. Tobacco smoking was classified as never smokers, smoking quitters because of reasons other than illness, quitters because of illness or current smokers (1–14, 15–24, or 25 more cigarettes or equivalent per day). For alcohol drinking, we asked about typical drinking frequency, type of alcoholic beverage consumed habitually, and volume of alcohol consumed on a typical drinking day in the past 12 months. Alcohol consumption was categorized as never regular or less than weekly drinkers, former weekly drinkers, weekly but not daily drinkers, daily drinkers: <30, 30–59, or ≥60 g/d of pure alcohol. Habitual intakes of 12 conventional food groups in the past 12 months were collected using a validated qualitative food frequency questionnaire.[e1] Days per week of consumption of red meat, fresh fruits, fresh vegetables, and preserved vegetables were assigned according to the midpoint of each frequency category (daily, 4–6 days per week, 1–3 days per week, monthly, or never or rarely). For tea consumption, we asked about usual frequency of tea drinking during the past 12 months. Participants who reported weekly consumption were asked about the usual temperature of the tea. Tea consumption was classified as less than daily drinkers, daily drinkers and preferring: warm tea, hot tea, or burning-hot tea. Questions about physical activity included the usual type and duration of activities in occupational, commuting, domestic, and leisure time in the past 12 months. Total physical activity levels (metabolic equivalent task [MET]-hours per day) were calculated by multiplying hours spent on each activity per day by corresponding physical intensity (MET), and then summing up the MET-h/d for all activities.

For second-hand smoking, we asked about hours of second-hand smoke exposure per week and years of living with a smoker. Participants were asked about years of living in the present residence and up to 2 previous residences. For each residence, we asked the participants about frequency of cooking and whether they heated their house in winter. Participants with a cooking facility in their house were asked whether the stove has a ventilation facility. We further asked the participants who cooked monthly or heated their house in winter about main cooking (eg, gas, coal, wood, electricity, or other) or heating fuels (ie, central heating, gas, coal, wood, electricity, or other). Solid fuels refer to coal and wood, and clean fuels refer to gas, electricity, and central heating. We categorized fuel types for cooking and heating in the baseline residence as clean fuels, solid fuels, or other fuels or no monthly cooking or heating in the winter. Years of solid fuel use at the past 3 residences were summed up.

Self-rated health was classified as excellent, good, fair, or poor. A family history of cancer refers to at least 1 of the parents or siblings having ever had any cancer. The full electronic questionnaire is available online at: https://www.ckbiobank.org/site/binaries/content/assets/resources/pdf/qs_baseline-final-from10june2004.pdf.

Assignment of Time-Varying and Time-Invariant Fine (≤2.5 μm) Particulate Matter Exposure

In the analyses of Cox model with a time-varying variable, an individual observation was split into multiple records by year (from wide data to long data). The $PM_{2.5}$ exposure of each record was assigned according to the average concentration of that year, when constructing the 1-year time-varying variable. For example, participant A was followed up from May 15, 2007 to July 26, 2012. The wide data of participant A is shown in Supplementary Table 1, which is transformed to long data of 6 records by year, as shown in Supplementary Table 2. The Cox model with the 1-year time-varying variable was performed using the long data. In the analysis of Cox model with a time-invariant variable, each participant had only 1 record, with the average concentration from 2005 to 2017 as the $PM_{2.5}$ exposure. When constructing 3-year or 5-year time-varying variables, an individual observation was still divided into multiple records by year. The $PM_{2.5}$ exposure of each record was assigned with an average concentration of the previous 3 (or 5) years. For example, when constructing the 3-year time-varying variable, the average concentration of 2005–2007 was assigned to the first record of participant A in Supplementary Table 2.

Estimated Population Attributable Fractions

The population attributable fraction (PAF) represents the proportion of incident cases in this population during follow-up can be prevented if the exposure of a risk factor reduced to an ideal level, assuming a causal relationship. For continuous risk factor ($PM_{2.5}$ and low BMI in this study), the PAF is defined as:

$$\mathrm{PAF} = \frac{\int_{x=l}^{u} HR(x)P(x)dx - 1}{\int_{x=l}^{u} HR(x)P(x)dx}$$

where $HR(x)$ is the hazard ratio as a function of exposure level x for risk factor with the reference level as l and the highest level as u; $P(x)$ is the distribution of exposure at x.

For binary risk factors, the PAF is defined as:

$$\mathrm{PAF} = \frac{P \times (HR - 1)}{P \times (HR - 1) + 1}$$

where P is prevalence and HR is the hazard ratio for the risk factor.

Supplementary Reference

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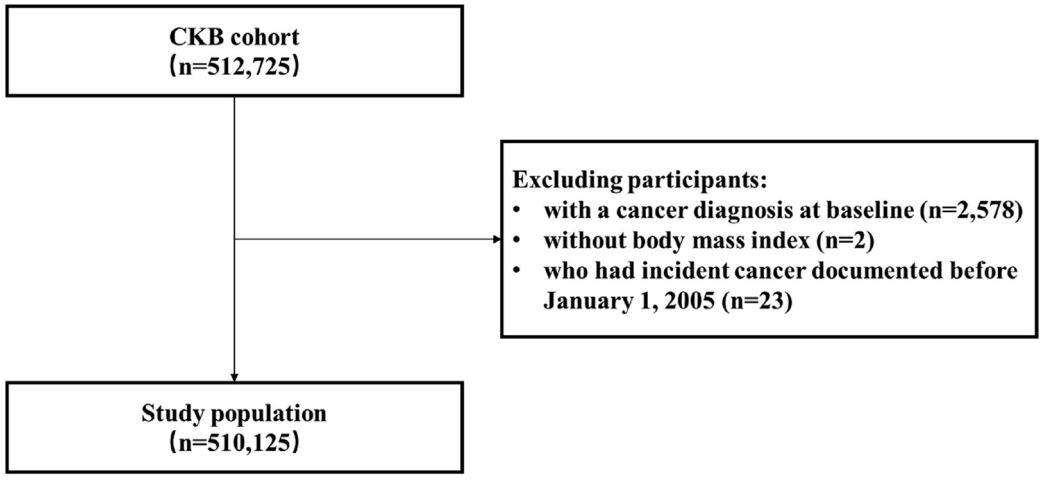
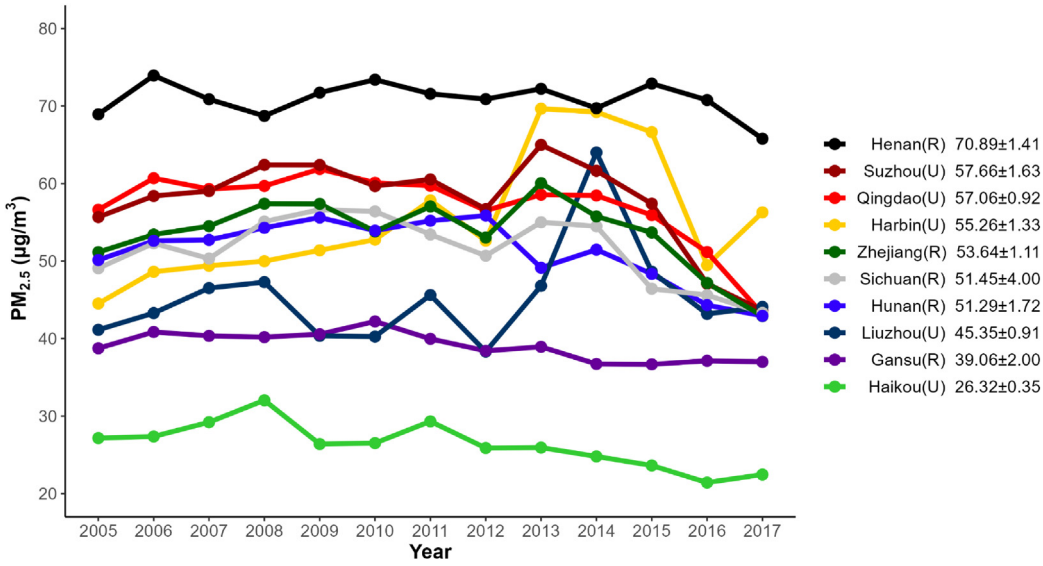
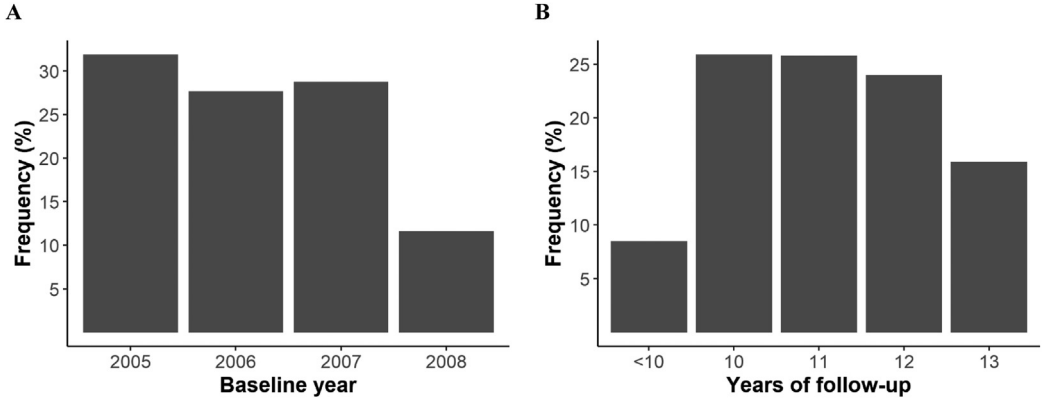


Supplementary Figure 1. Flow diagram of study participants.



Supplementary Figure 2. Annual average $PM_{2.5}$ concentration ($\mu g/m^3$) from 2005 to 2017 among 10 China Kadoorie Biobank study areas. "U" or "R" in the parentheses indicates whether the area is urban or rural. Values in the legend are mean ± SD of $PM_{2.5}$ concentrations from 2005 to 2017 in each area.



Supplementary Figure 3. Distribution of (*A*) baseline year and (*B*) years of follow-up.

Supplementary Table 1. Wide Data of Participant A

Record	Participant	Start time	End time	Average concentration of $PM_{2.5}$, $\mu g/m^3$					
				2007	2008	2009	2010	2011	2012
1	A	May 15, 2007	July 26, 2012	57.6	59.3	60.4	63.5	65.7	67.8

Supplementary Table 2. Long Data of Participant A

Record	Participant	Start time	End time	1-y time-varying variable of $PM_{2.5}$, $\mu g/m^3$
1	A	May 15, 2007	December 31, 2007	57.6
2	A	December 31, 2007	December 31, 2008	59.3
3	A	December 31, 2008	December 31, 2009	60.4
4	A	December 31, 2009	December 31, 2010	63.5
5	A	December 31, 2010	December 31, 2011	65.7
6	A	December 31, 2011	December 26, 2012	67.8

NOTE. In the analysis of Cox model with a time-invariant variable, each participant had only 1 record, with the average concentration from 2005 to 2017 as the $PM_{2.5}$ exposure.

Supplementary Table 3. Sensitivity Analyses for the Association of Esophageal Cancer Incidence with per 10-$\mu g/m^3$ Increase in $PM_{2.5}$

Variable	Cases, n	HR (95% CI)
Using 3-y average $PM_{2.5}$ as time-varying variable	2550	1.25 (1.07–1.46)
Using 5-y average $PM_{2.5}$ as time-varying variable	2550	1.37 (1.15–1.64)
Using average $PM_{2.5}$ from 2005 to 2017	2550	1.46 (1.20–1.77)
Excluding incident cases occurred in the first year of follow-up	2319	1.14 (1.01–1.28)
Excluding incident cases occurred in the first 3 years of follow-up	1910	1.10 (0.97–1.24)
Excluding participants in Henan	1265	1.16 (1.02–1.33)
Adding a random intercept for clinic locations	2550	1.16 (1.03–1.30)
Adding a nested random intercept for clinic locations and study areas	2550	1.12 (1.02–1.24)
Using age as time scale	2550	1.14 (1.02–1.26)
Only considering ESCC cases as occurrence of the study outcome	721	1.25 (1.02–1.54)

NOTE. The models were adjusted for age (years), sex, education (no formal school, primary school, middle school, or high school or above), household income ($<$10,000, 10,000–19,999, or $\geq$20,000 Chinese renminbi/y), occupation (farmers, factory workers, administrators or managers, technical workers, sales or service workers, self-employed, or others), tobacco smoking (never smokers, smoking quitters because of reasons other than illness, quitters because of illness or current smokers: 1–14, 15–24, or $\geq$25 cigarettes or equivalent per day), alcohol consumption (never regular or less than weekly drinkers, former weekly drinkers, weekly but not daily drinkers, daily drinkers: $<$30, 30–59, or $\geq$60 g/d of pure alcohol), consumption of red meat, fresh fruits, fresh vegetables, and preserved vegetables (days per week; assigning according to the midpoint of each frequency category), consumption of tea and hot tea preference (less than daily drinkers, daily drinkers and preferring: warm tea, hot tea, or burning-hot tea), total physical activity levels (metabolic equivalent of task-h/d), leisure sedentary time (h/d), fuel types for cooking and heating at baseline residence (clean fuels, solid fuels, or other fuels or no monthly cooking or heating in the winter), duration of solid fuel use at the past three residences (years), cookstove ventilation at baseline residence (yes or no), hours of exposure to second-hand smoke (h/d), duration of living with a smoker (years), BMI (kg/m^2), waist-to-hip ratio, self-rated health status (excellent, good, fair, or poor), and family history of cancer (yes or no).