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Long-term exposure to ambient fine particles and gastrointestinal cancer mortality in Taiwan: A cohort study

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ABSTRACT

Background: Information on the association between long-term exposure to $PM_{2.5}$ and gastrointestinal cancer mortality is scarce.
Objectives: This study investigated the association between long-term exposure to $PM_{2.5}$ and deaths from gastrointestinal cancer and its subtypes in adults in Taiwan.
Methods: A total of 385,650 Taiwanese adults (≥18 years old) jointed a standard medical examination program between 2001 and 2014 and were followed up until 2016. Their vital data were obtained from the National Death Registry maintained by the Ministry of Health and Welfare in Taiwan. We estimated the ambient $PM_{2.5}$ concentration at individual's address utilising a satellite-based spatiotemporal model at a resolution of 1 km^2. Cox proportional hazard regression model was used to investigate the associations between ambient $PM_{2.5}$ and deaths from gastrointestinal, stomach, colorectal and liver cancers.
Results: We found that each 10 $\mu g/m^3$ increase in $PM_{2.5}$ was associated with an increased hazard risk (HR) of 1.09 (95% confidence interval (CI): 1.03–1.16) and 1.13 (95%CI: 1.02–1.24) in deaths from gastrointestinal and liver cancers, respectively. The association between $PM_{2.5}$ and death from colorectal cancer was marginally statistically significant [HR: 1.13 (95%CI: 1.00–1.26)]. We did not find significant associations between $PM_{2.5}$ and mortality from stomach cancer.
Conclusions: Long-term exposure to ambient $PM_{2.5}$ was associated with an increased risk of deaths from gastrointestinal cancers, liver cancer and also potentially colorectal cancer. Air pollution control strategies are necessary to reduce the burden of gastrointestinal cancer.

1. Introduction

The Global Burden of Disease study estimated that air pollution was linked to 4.9 million deaths worldwide in 2017 and that most of these deaths (4.6 million) were attributable to particulate matter (PM) pollution (Seattle 2018). Air pollution was also classified as a Group I carcinogen by the International Agency for Research on Cancer (IARC) in 2013 (Loomis et al., 2013). Fine particles ($PM_{2.5}$), with their toxic components and penetrability into various human organs, may be associated with a much wider spectrum of morbidity and mortality outcomes.

Previous studies on the effects of air pollution on cancer have mainly focused on total cancer mortality and a limited range of cancers, such as lung cancer. Although some of these studies have also reported

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associations between air pollution and gastrointestinal cancer (Ancona et al., 2015; Deng et al., 2017; Fernandez-Navarro et al., 2017; Garcia-Perez et al., 2013; Jerrett et al., 2005; Nagel et al., 2018; Pan et al., 2016; Turner et al., 2017; Weinmayr et al., 2018; Wong et al., 2016), investigations on gastrointestinal cancer have rarely been thorough and their results were inconsistent. Furthermore, a few of them (Nagel et al., 2018; Turner et al., 2017; Weinmayr et al., 2018; Wong et al., 2016) examined $PM_{2.5}$ air pollution at individuals' addresses and were conducted in Asia (Wong et al., 2016), where most countries are experiencing serious air pollution. Information on subtypes of gastrointestinal cancer is even scarcer. A short review of these studies was presented in Supplementary Table 1.

Therefore, we conducted this study to investigate the effects of long-term exposure to ambient $PM_{2.5}$ on the deaths from any types and subtypes of gastrointestinal cancer in a large cohort of 368,986 Taiwanese adults between 2001 and 2016.

2. Materials and methods

2.1. Study population and design

The participants were from a large ongoing cohort initiated by the MJ Health Management Institution. We have described the cohort details in our previous publications (Chang et al., 2016; Guo et al., 2018). In brief, the institution has provided Taiwan residents a standard medical screening programme through a paid membership since 1994. Members are encouraged to visit the institution regularly and receives a series of medical examinations such as anthropometry measurements, spirometry, as well as and blood and urine tests. Information on demographics, lifestyle habits and medical history are also collected via a standard self-administered questionnaire during each visit. A written informed consent form is signed by each participant prior to the medical examination. The Joint Chinese University of Hong Kong - New Territories East Cluster Clinical Research Ethics Committee (2016.672) and the Institutional Review Board of Academia Sinica on Biomedical Science Research (AS-IRB-BM16054) approved this study.

The procedure of participant selection is shown in Fig. 1. A total of 425,115 adults (≥18 years old) were recruited between 2001 and 2014, when ambient $PM_{2.5}$ concentration was available. We excluded 39,465 participants due to incomplete information (2,950 for missing $PM_{2.5}$ concentrations due to missing addresses and 36,515 for missing covariates). The vital statuses of the remaining 385,650 participants were followed up until December 2016 and were included in the analysis.

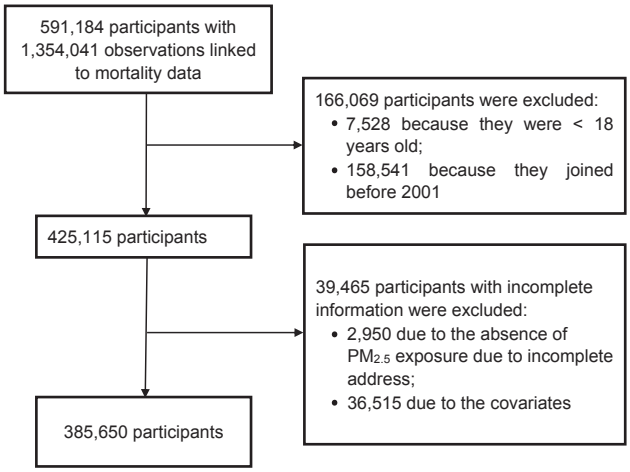

Fig. 1. Procedure of participant selection for the gastrointestinal cancer mortality study.

2.2. $PM_{2.5}$ exposure assessment

The exposure assessment method has been described in detail elsewhere (Lin et al., 2015, 2018). In brief, a satellite-based spatio-temporal model was developed to estimate ambient $PM_{2.5}$ concentration using the aerosol optical depth (AOD) data at a resolution of 1 km^2. The AOD data was from the Moderate Resolution Imaging Spectroradiometer instruments aboard the Terra and Aqua satellites, which were launched by the U.S. National Aeronautics and Space Administration. To validate the model, we compared the estimated concentration with the $PM_{2.5}$ data from > 70 monitoring stations across Taiwan. The corresponding correlation coefficients ranged from 0.72 to 0.83(Guo et al., 2018).

The annual average concentrations of $PM_{2.5}$ were calculated, and estimated $PM_{2.5}$ concentrations were assigned to the participants based on their geocoded addresses. The two-year average $PM_{2.5}$ at the year of medical examination and the previous year was used as an indicator for the long-term exposure in this study.

2.3. Outcome measurements

The health outcomes included: (1) deaths from total gastrointestinal cancer and (2) deaths from subtypes of gastrointestinal cancer. The vital statuses of the participants were obtained by matching each participant's identification number with those from the national death registry database maintained by the Health and Welfare Data Science Centre of the Ministry of Health and Welfare of Taiwan (Welfare 2017). Gastrointestinal cancer mortality and its subtypes were identified using the corresponding International Classification of Diseases (ICD) codes as follows: deaths from gastrointestinal cancer (i.e., malignant neoplasms of digestive organs – ICD-9: 150–159 or ICD-10: C15–C26), stomach cancer (i.e., malignant neoplasm of stomach – ICD-9: 151 or ICD-10: C16), colorectal cancer (i.e., malignant neoplasm of colon, rectosigmoid junction, rectum, anus and anal canal – ICD-9: 153–154 or ICD-10: C18–C21) and liver cancer (i.e., malignant neoplasm of liver and intrahepatic bile ducts – ICD-9: 155 or ICD-10: C22).

2.4. Covariates

The details of the medical examinations and quality control have been described in the MJ technical report and previous publications (Chang et al., 2016; Guo et al., 2018). In brief, we measured body height and weight while the participants were wearing light clothing without shoes. An overnight-fasting blood sample was taken in the morning. We utilised an automatic biochemical analyser (7150, Hitachi, Tokyo, Japan) to measure the plasma glucose and lipids profile of the participants. The blood pressure of the participants in a seated position were measured utilising an auto-sphygmomanometer (Citizen CH-5000, Tokyo, Japan). We used a standard self-administered questionnaire to collect the information on their demographics, lifestyle habits, and medical history.

We included the following covariates: age (years), sex (male or female), education level (middle school or lower [< 10 years], high school [10–12 years old], college or above [≥13 years old]), body mass index (BMI, calculated as weight divided by height squared [kg/m^2]), cigarette smoking (never, former [previously a smoker, but quit later] or current [> once/week]), alcohol drinking (seldom/never [< once/week], occasional [one to two times/week] or regular [≥ three times/week]), physical activity (inactive, light [e.g., normal walking], moderate [e.g., normal swimming] or high and vigorous [e.g., running]), vegetable or fruit intake (seldom [< 1 serving/day], moderate [1–2 servings/day] or frequent [> 2 servings/day]), occupational exposure to dust or solvent (yes or no), season (spring: March to May; summer: June to August; autumn: September to November; or winter: December to February) and year of enrolment.

2.5. Statistical analysis

Cox proportional hazard regression model was used for data analyses and the aforementioned covariates were included in the model to control for their potential effects. The proportional hypothesis was verified using Kaplan-Meier survival curves and Schoenfeld residuals plots. Effect estimates were presented as hazard risk (HR) with a 95% confidence interval (CI) for each 10 μg/m^3 increase in $PM_{2.5}$. The $PM_{2.5}$ concentrations were also categorised into quartiles for data analysis, with the first quartile as the reference.

To examine the stability of the results, we conducted a series of sensitivity analyses including: (1) adjustment for age, sex, education, BMI, cigarette smoking, alcohol drinking, physical activity, vegetable and fruit intake, occupational exposure, hypertension (defined as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg or self-reported hypertension), diabetes (defined as fasting blood glucose ≥ 126 mg/dl or self-reported physician-diagnosed diabetes), dyslipidaemia (defined as total cholesterol ≥ 240 mg/dl, triglyceride ≥ 200 mg/dl or HDL-C < 40 mg/dl), self-reported physician-diagnosed CVDs, season and year of enrolment to examine whether adjusting for potential mediators (or health conditions) might bias the main results; (2) use of annual $PM_{2.5}$ concentrations at the year of medical examinations, and three- and five-year averages of $PM_{2.5}$ concentrations to assess the stability of effect estimates of $PM_{2.5}$ exposure; (3) exclusion of individuals who were followed up for fewer than two, five and seven years, to control for the delayed effects of $PM_{2.5}$ air pollution on mortality (two years of incubation period or five-years survival rate); (4) exclusion of study participants who had a history of cancer at the year of enrolment, to minimise the potential confounding effects of this co-mobility; and (5) the participants enrolled before 2001 and substituting the unavailable $PM_{2.5}$ by the 6-year average of $PM_{2.5}$ estimates from 2001 to 2006.

To investigate the potential modifying effects, we further conducted stratified analyses by sex (male vs. female), age (18–65 years old vs. ≥ 65 years old), cigarette smoking (never vs. ever), BMI (< 25 kg/m^2 vs. ≥ 25 kg/m^2), education (high school or lower vs. college or higher), alcohol drinking (seldom vs. occasional/regular) and physical activity (inactive or low vs. moderate or high).

All statistical analyses were conducted using R survival package (version 3.5.2). The $PM_{2.5}$ effects and interaction terms were treated as statistically significant at a two-tailed level of 0.05.

3. Results

In this study, 385,650 participants were enrolled between January 2001 to December 2014 and all were followed up until December 2016 (the censoring date). The mean follow-up duration was 10.6 years with a standard deviation (SD) of 3.9 years, yielding a total of 49.2 million person-years of follow-up. Table 1 shows the characteristics of the study participants by different levels of $PM_{2.5}$ exposure. Approximately half of the participants (48.56%) were males and 64.33% attained an education level of college or above. The majority of the participants had never smoked, never/seldom consumed alcohol and were inactive/had a low level of physical activity. The mean value of two-year average $PM_{2.5}$ was 26.57 μg/m^3 (SD: 7.60) with an interquartile range (IQR) of 21.63–28.37 μg/m^3. The mean value (SD) of the 1st, 2nd 3rd and 4th quartile of $PM_{2.5}$ concentration was 19.55 (1.87), 22.83 (0.66), 25.53 (1.15), and 38.37 (4.70) ug/m^3, respectively (Table 1). The baseline characteristics of the participants died from all and subtypes of gastrointestinal cancer are presented in Supplementary Table 2. Table 2 shows the distribution of $PM_{2.5}$ concentration over the study years.

A total of 1,591 deaths from gastrointestinal cancer were identified in this study, among which deaths from liver cancer ranked as the leading cause (Table 1). The participants who died from gastrointestinal cancer generally had a lower education and reported higher rates of cigarette smoking and alcohol drinking at baseline. The mortality rate for gastrointestinal cancer, stomach cancer, colorectal cancer and liver cancer was 38.8, 5.3, 10.1 and 14.9 per 100,000 person-years, respectively (Table 3).

Table 3 shows the associations between long-term exposure to ambient $PM_{2.5}$ and gastrointestinal cancer mortality. Each 10 μg/m^3 increase in $PM_{2.5}$ was associated with an increased risk of 9% (HR [95% CI]: 1.09 [1.03–1.16]) and 13% (1.13 [1.02–1.24]) in deaths from gastrointestinal and liver cancers, respectively, after adjusting for all covariates mentioned above. $PM_{2.5}$ was also associated with deaths from colorectal cancer with a HR of 1.13 (95%CI: 1.00–1.26) with marginal statistical significance. No significant associations were observed for stomach cancer mortality. The sensitivity analyses generally yielded similar results except for Sensitivity analysis 7 (Supplementary Table 3). The associations between $PM_{2.5}$ and gastrointestinal cancer mortality were relatively larger in the participants who were followed up ≥ 7 years as compared to the main findings.

Table 4 and Supplementary Table 4 show the results of the subgroup analyses. Interaction tests indicate the significant modifying effects of cigarette smoking on the associations between $PM_{2.5}$ and mortality from stomach cancer (P value for the interaction term < 0.001) (Table 4). No significant modifying effects were observed for the other factors (all P values > 0.05).

4. Discussion

In this cohort consisting of 385,650 adults aged ≥ 18 years, we found that long-term exposure to ambient $PM_{2.5}$ is associated with deaths from gastrointestinal cancer. Each 10 μg/m^3 increase in $PM_{2.5}$ was associated with a 9% increase in the risk of gastrointestinal cancer mortality. The associations between $PM_{2.5}$ and liver and colorectal cancer mortality was statistically significant. We did not observe significant associations between $PM_{2.5}$ and mortality from stomach cancer in this study.

Our study has several important strengths. First, we investigated the $PM_{2.5}$-gatrointestinal cancer mortality associations in a general Han Chinese population with a wide range of age (from 18 to 102 years old) in a highly polluted area. Second, the large sample size and the relatively long follow-up duration sufficiently powered the study to discern the small effects of ambient $PM_{2.5}$ on gastrointestinal cancer mortality. The large sample size also enabled us to explore the subtypes of gastrointestinal cancer mortality. Also, $PM_{2.5}$ concentrations were estimated based on a spatiotemporal model to capture ground-level exposure. This technology overcomes the spatial coverage problems of traditional method using data from air pollution monitoring stations, although some recent studies have improved the resolution of air pollution assessment.

Information on air pollution and gastrointestinal cancer mortality is limited. We identified a few cohort studies (Ancona et al., 2015; Deng et al., 2017; Jerrett et al., 2005; Turner et al., 2017; Wong et al., 2016) and one meta-analysis (Kim et al., 2018) that reported information on the associations between air pollution and mortality from gastrointestinal cancer and its subtypes. Among these studies, two (Jerrett et al., 2005; Wong et al., 2015) included the mortality from gastrointestinal cancer. It is difficult to directly compare the air pollution-related risks of gastrointestinal cancer mortality with those of other studies, given that air pollutants, study designs and target populations are different. The study in Hong Kong (Wong et al., 2016) found a higher risk (22%) of gastrointestinal cancer mortality for every 10 μg/m^3 increase in $PM_{2.5}$, but they did not explore the $PM_{2.5}$ effects on subtypes of gastrointestinal cancer mortality. The HR in the Hong Kong study was higher than that in our study (1.22 vs. 1.09). The possible reasons for this difference include the targeting of elderly participants in the Hong Kong study, as well as the higher $PM_{2.5}$ concentrations in Hong Kong and the different exposure-assessment methods used. However, Jerrett et al (Jerrett et al., 2005) did not find statistically significant associations between air pollution and mortality from

Table 1
Baseline characteristics of the participants by different levels of $PM_{2.5}$ exposure.

	All participants (n = 385,650)	1st quartile [a] (n = 96,595)	2nd quartile[a] (n = 95,936)	3rd quartile[a] (n = 96,782)	4th quartile[a] (n = 96,337)
Age (years)	39.55 (12.95)	40.15 (13.25)	39.03 (12.61)	38.74 (12.61)	40.26 (13.25)
Male (n, %)	187,275 (48.56)	46,256 (47.89)	46,433 (48.4)	47,044 (48.61)	47,542 (49.35)
Education (n, %)					
Lower than high school	60,721 (15.75)	16,521 (17.1)	12,781 (13.32)	13,328 (13.77)	18,091 (18.78)
High school	76,822 (19.92)	20,049 (20.76)	17,099 (17.82)	17,875 (18.47)	21,799 (22.63)
College or above	248,107 (64.33)	60,025 (62.14)	66,056 (68.85)	65,579 (67.76)	56,447 (58.59)
Cigarette smoking (n, %)					
Never	284,709 (73.83)	70,802 (73.3)	70,902 (73.91)	71,226 (73.59)	71,779 (74.51)
Former	21,996 (5.70)	5,975 (6.19)	5,364 (5.59)	5,278 (5.45)	5,379 (5.58)
Current	78,945 (20.47)	19,818 (20.52)	19,670 (20.5)	20,278 (20.95)	19,179 (19.91)
Alcohol drinking (n, %)					
Never/seldom	331,361 (85.92)	82,884 (85.81)	82,861 (86.37)	83,436 (86.21)	82,180 (85.30)
Former	35,973 (9.33)	9,072 (9.39)	8,821 (9.19)	8,959 (9.26)	9,121 (9.47)
Current	18,316 (4.75)	4,639 (4.80)	4,254 (4.43)	4,387 (4.53)	5,036 (5.23)
Physical activity (n, %)					
Inactive	65,663 (17.03)	17,421 (18.04)	15,278 (15.93)	15,156 (15.66)	17,808 (18.49)
Low	213,922 (55.47)	52,367 (54.21)	53,321 (55.58)	54,847 (56.67)	53,387 (55.42)
Medium	72,444 (18.78)	18,027 (18.66)	18,742 (19.54)	18,495 (19.11)	17,180 (17.83)
High-vigorous	33,621 (8.72)	8,780 (9.09)	8,595 (8.96)	8,284 (8.56)	7,962 (8.26)
Vegetable intake (n, %)					
Seldom	55,368 (14.36)	14,148 (14.65)	13,909 (14.5)	14,501 (14.98)	12,810 (13.30)
Moderate	227,675 (59.04)	56,788 (58.79)	56,859 (59.27)	57,206 (59.11)	56,822 (58.98)
Frequent	102,607 (26.61)	25,659 (26.56)	25,168 (26.23)	25,075 (25.91)	26,705 (27.72)
Fruit intake (n, %)					
Seldom	133,332 (34.57)	33,541 (34.72)	33,860 (35.29)	35,049 (36.21)	30,882 (32.06)
Moderate	206,978 (53.67)	51,780 (53.61)	51,059 (53.22)	51,162 (52.86)	52,977 (54.99)
Frequent	45,340 (11.76)	11,274 (11.67)	11,017 (11.48)	10,571 (10.92)	12,478 (12.95)
Occupational exposure (n, %)	30,663 (7.95)	7,377 (7.64)	6,561 (6.84)	7,066 (7.30)	9,659 (10.03)
Body mass index (kg/m^2)	23.03 (3.71)	23.07 (3.71)	22.96 (3.70)	22.94 (3.72)	23.14 (3.69)
$PM_{2.5}$ ($\mu g/m^3$)	26.57 (7.60)	19.55 (1.87)	22.83 (0.66)	25.53 (1.15)	38.37 (4.70)

Note: Abbreviations: $PM_{2.5}$, particulate matter with aerodynamic diameter $<$ 2.5 μm.
The statistics are shown as mean (standardized deviation, SD) for continuous variables and count (percentage, %) for categorical variables.
[a] The 1st quartile of $PM_{2.5}$ is $<$ 21.63 $\mu g/m^3$; the 2nd quartile has a range of 21.63–23.90 $\mu g/m^3$; the 3rd quartile has a range of 23.90–28.37 $\mu g/m^3$; and the 4th quartile of $PM_{2.5}$ is $\geq$28.37 $\mu g/m^3$.

gastrointestinal cancers. The corresponding relative risk (RR) was 1.29 (95%CI: 0.87–1.90) for every 10 $\mu g/m^3$ increase in $PM_{2.5}$. The small number of cancer cases (429) in their study may partially explain this lack of association.

Liver cancer was the second leading cause of cancer death in Taiwan in 2017 and ranked sixth worldwide in 2018 (Bray et al., 2018). In this study, we found an increased risk of 13% [HR (95%CI): 1.13 (1.02–1.24)] in liver cancer mortality for each 10 $\mu g/m^3$ increase in $PM_{2.5}$ (Table 3). Our results are in line with the results from another study in Taiwan by Pan et al. (2016), but the risk magnitude reported by Pan et al was much larger than our finding (15.24 vs. 1.13 for each 10 $\mu g/m^3$ increase in $PM_{2.5}$). We are not sure the exact reason for the difference. The relatively small sample size in Penghu Islets (N = 8,888) might contribute to the difference or the estimated effect by Pan et al might be an outlier. Deng et al. (2017) also conducted a study based on 20,221 patients with HCC and their results showed that each 5 $\mu g/m^3$ increment in $PM_{2.5}$ was associated with 5–31% higher risk of HCC-related mortality among patients with different stages of liver cancer. However, three studies conducted in America (Turner et al., 2017), Italy (Ancona et al., 2015) and Europe (Pedersen et al., 2017) did not report significant associations between ambient air pollution and liver cancer mortality or incidence. The lower level of air pollution and smaller number of cases possibly contributed to the insignificant associations. Regardless of the statistical insignificance, the

Table 2
Distribution of two-year average $PM_{2.5}$ concentrations ($\mu g/m^3$) by year in Taiwan.

Year	N	Mean (SD)	Minimum	First quartile	Median	Third quartile	Maximum
2001	62,507	24.96 (7.35)	5.55	20.11	22.50	28.15	43.50
2002	46,370	26.61 (8.26)	7.30	21.07	23.53	34.64	44.76
2003	32,462	28.88 (8.41)	7.63	23.15	25.89	36.02	48.72
2004	32,111	29.82 (8.71)	6.63	23.64	26.54	37.54	49.78
2005	31,461	27.31 (7.85)	6.40	22.20	24.45	27.36	49.04
2006	28,695	26.78 (6.81)	7.49	22.61	24.62	27.44	48.79
2007	28,207	26.94 (6.65)	7.72	22.65	24.99	27.77	50.34
2008	24,528	26.92 (6.81)	7.31	22.56	24.86	27.53	48.78
2009	17,176	27.26 (7.13)	8.09	22.48	25.15	30.00	46.44
2010	20,786	25.81 (7.16)	6.18	21.47	23.32	26.28	46.14
2011	18,809	25.33 (7.00)	6.01	20.88	23.13	25.64	48.18
2012	21,281	24.43 (6.19)	6.32	20.41	22.82	25.34	46.08
2013	16,091	23.65 (5.81)	6.27	19.83	22.27	25.34	43.06
2014	5,166	24.53 (4.60)	7.45	21.33	24.13	26.18	42.82
All	385,650	26.57 (7.60)	5.55	21.63	23.90	28.37	50.34

Table 3
Associations of ambient $PM_{2.5}$ with gastrointestinal cancer mortality.

Cancer mortaliy[a]	Counts/mortality rate[b]	Second quartile[c]		Third quartile[c]		Fourth quartile[c]		Every 10 μg/m^3	
		Hazard ratio	*P*	Hazard ratio	*P*	Hazard ratio	*P*	Hazard ratio	*P*
Gastrointestinal	1,591 (38.8)	1.00 (0.87, 1.16)	0.946	0.93 (0.80, 1.08)	0.314	1.16 (1.02, 1.33)	0.021	1.09 (1.03, 1.16)	0.003
Stomach	216 (5.3)	0.96 (0.67, 1.38)	0.832	0.76 (0.51, 1.15)	0.193	0.90 (0.63, 1.28)	0.556	0.97 (0.82, 1.15)	0.737
Colorectal	416 (10.1)	1.02 (0.77, 1.35)	0.878	1.07 (0.80, 1.43)	0.631	1.24 (0.96, 1.60)	0.102	1.13 (1.00, 1.26)	0.046
Liver	611 (14.9)	1.03 (0.82, 1.29)	0.824	0.87 (0.68, 1.11)	0.258	1.23 (1.00, 1.51)	0.053	1.13 (1.02, 1.24)	0.015

Note:
[a] The effects were estimated after adjusting for age, sex, education, BMI, cigarette smoking, alcohol drinking, physical activity, vegetable and fruit intake, occupational exposure, season and year of enrolment.
[b] The number of deaths and incident rate per 100,000 person-years.
[c] The reference level is the 1st quartile of $PM_{2.5}$ (< 21.63 μg/m^3); the 2nd quartile has a range of 21.63–23.90 μg/m^3; the 3rd quartile has a range of 23.90–28.37 μg/m^3; and the 4th quartile of $PM_{2.5}$ is ≥28.37 μg/m^3.

Table 4
Stratified analyses of associations between $PM_{2.5}$ and gastrointestinal cancer mortality by sex, age and smoking status.

Effect modifiers[a]	Gastrointestinal		Stomach		Colorectal		Liver	
	Hazard ratio	*P*	Hazard ratio	*P*	Hazard ratio	*P*	Hazard ratio	*P*
Sex		0.721[b]		0.457[b]		0.263[b]		0.121[b]
Male	1.08 (1.00, 1.17)	0.040	1.04 (0.84, 1.29)	0.710	1.19 (1.02, 1.40)	0.030	1.07 (0.96, 1.20)	0.228
Female	1.11 (1.01, 1.23)	0.034	0.87 (0.66, 1.15)	0.334	1.06 (0.89, 1.26)	0.497	1.26 (1.05, 1.50)	0.011
Age		0.225[b]		0.910[b]		0.743[b]		0.234[b]
18–65 years	1.06 (0.99, 1.14)	0.106	0.99 (0.80, 1.23)	0.930	1.10 (0.95, 1.27)	0.202	1.08 (0.96, 1.21)	0.207
≥65 years	1.12 (1.01, 1.24)	0.036	0.92 (0.70, 1.20)	0.525	1.14 (0.93, 1.40)	0.204	1.21 (1.02, 1.44)	0.031
Cigarette smoking		0.421[b]		0.009[b]		0.685[b]		0.359[b]
Never	1.08 (1.00, 1.17)	0.044	0.81 (0.65, 1.02)	0.072	1.09 (0.95, 1.26)	0.204	1.11 (0.97, 1.27)	0.136
Ever	1.11 (1.01, 1.22)	0.030	1.27 (0.98, 1.65)	0.069	1.21 (0.97, 1.50)	0.084	1.15 (1.00, 1.31)	0.049

Note: Abbreviations: BMI, body mass index; $PM_{2.5}$, particulate matter with aerodynamic diameter < 2.5 μm.
[a] The effects were estimated by adjusting for demographic factors (age, sex, and education), lifestyles (smoking status, alcohol drinking, physical activity, vegetable and fruit intake, and occupational exposure), season, and year of enrolment, except for the corresponding modifiers.
[b] P values represent the interaction effects between $PM_{2.5}$ and possible modifiers.

risk magnitude in the study by Turner et al. (2017) was comparable with ours (1.11 vs. 1.13 for each 10 μg/m^3 increase in $PM_{2.5}$).

Colorectal cancer was one of the top five leading causes of cancer deaths in both Taiwan and the world in 2018 (Bray et al., 2018). We found an association between $PM_{2.5}$ and mortality from colorectal cancer with a borderline statistical significance [HR: 1.13 (95%CI: 1.00–1.26)] (Table 3). Turner et al. (2017) did not find a significant association of mortality with ambient $PM_{2.5}$, but the effect magnitude was comparable with our findings [HR is 1.09 (95%CI: 1.00–1.19) for each 10 μg/m^3 increase in $PM_{2.5}$]. They also observed that the mortality increased 6% (95%CI: 2–10%) for each 6.5 ppb increase in NO_2. Another study in Denmark (Raaschou-Nielsen et al., 2011) showed that NOx was not associated with the incidence of colon or rectal cancer with HRs ranging from 0.80 to 0.93 for each 100 μg/m^3 increase in NO_x. Other studies in US (Mills et al., 1991) and in Italy (Ancona et al., 2015) did not observe significant associations between other air pollutants (i.e., total suspended particles, ozone, PM_{10} and SO_x) and colorectal cancer, either.

There were no associations found between $PM_{2.5}$ and stomach cancer mortality in our study, which is consistent with two previous cohort studies on mortality (Ancona et al., 2015; Turner et al., 2017) and one on morbidity (Raaschou-Nielsen et al., 2011). However, the European Study of Cohorts for Air Pollution Effects (ESCAPE) study (Weinmayr et al., 2018) showed that the incidence of stomach cancer was only associated with the increase of $PM_{2.5}$ with sulphur components based on ten cohorts in six European countries [HR was 1.93 (95%CI: 1.13–3.27) for each 200 ng/m^3 increase in $PM_{2.5}$ with sulphur]. Other studies of miners (Kreuzer et al., 2012; Santibañez et al., 2012) also found positive associations between stomach cancer and dust in occupational settings. Further studies are warranted to investigate the associations between $PM_{2.5}$ and stomach cancer.

There was little information on modifiers for the associations between air pollution and gastrointestinal cancer. Therefore, we conducted subgroup analyses to explore the modifying effects of a series of factors including sex, age, cigarette smoking, BMI, education, alcohol drinking, and physical activity. No significant modifying effects were observed except for cigarette smoking for stomach cancer (Table 4). Statistical significance was not consistent across the subgroups (i.e., associations were statistically significant in some subgroups but not in others). This might have been due to the smaller sample size of subgroups. In addition, multiple testing and multiple cancer sites may link to significant associations that might be due to chance (Turner et al., 2017). This suggests that future studies on the associations in individuals who are susceptible to air pollution with regard to gastrointestinal cancers are needed.

The potential mechanism for the associations between $PM_{2.5}$ and gastrointestinal cancer mortality is complex and remains unclear. However, $PM_{2.5}$ may contain various toxic elements including heavy metals and other carcinogens, which could trigger the development and progression of cancer. In addition, at the molecular level, the genotoxic effects of PM may lead to defects in DNA repair, replication and mutations (Manju et al., 2008). At the cellular level, PM may induce cell damage and apoptosis (Waisberg et al., 2003). Other hypotheses are based on oxidative stress and inflammation, where PM may increase oxidative stress by generating oxidants and free radicals and also by consumption of antioxidants and enzymes (Kelly 2003). Besides, oxidative stress was found to be further associated with many types of cancer, including gastrointestinal cancer (Kruk and Y Aboul-Enein, 2017). It is also well known that exposure to air pollution can increase inflammation levels in the human body, with tumour-associated macrophages produced in inflammatory reactions, which predisposes an individual to a cancerous state (Duncan et al., 1998). In the digestive

system, PM pollutants may enter the digestive tract, alter the immune response and affect gut microbiota and epithelial cells (Beamish et al., 2011; Wong et al., 2016). In addition, the adverse effects of air pollution on biological ageing, the nervous system, smooth muscles and the immune system may also play an important role (IARC 2013; Turner et al., 2016).

The results of our study should be interpreted cautiously with awareness of certain limitations. First, we considered only ambient $PM_{2.5}$ with other pollutants such as gases excluded. However, previous studies have noted a high temporal and spatial correlation between $PM_{2.5}$ and other gaseous pollutants (although this might not always be appropriate), and a multiple pollutant model might not be appropriate (Crouse et al., 2015). Second, the $PM_{2.5}$ concentrations were assigned to the participants' addresses, but the activity patterns of the participants (such as daily transportation) were not recorded. More advanced technology, such as the use of real-time wearable sensors, is needed to capture such details of exposure in future studies. Third, our participants joined the health-screening programme through paid membership and they generally had a relatively high socioeconomic status. The national mortality rate of gastrointestinal cancer was higher than the mortality rate in this study [the average of annual mortality rate of stomach, colorectal and liver cancer in Taiwan was 10.3, 19.9 and 33.2 per 100,000 persons, respectively between 2001 and 2016 (Welfare 2017)]. Thus, care should be taken when generalising the results to other populations. However, this study mainly aimed to investigate the associations between $PM_{2.5}$ and gastrointestinal cancer mortality rather than assess the number of deaths or mortality rate. Therefore, this may not significantly bias our main findings. Fourth, the outcome was gastrointestinal cancer mortality rather than morbidity, but for cancers with a long survival duration (such as colorectal cancer, which had a 5-year survival rate of 62.6% in 2010–2014) (Allemani et al., 2018), using mortality as an outcome might underestimate the associations (Turner et al., 2017). This is possibly because the cancer might not be diagnosed as the underlying death cause, and the number of cases will therefore decrease. However, using mortality as an endpoint may approximate a morbidity endpoint for rapidly fatal cancer (Turner et al., 2017), such as liver cancer (5-year survival rate is 27.9%) (Allemani et al., 2018). This is possibly why we observed more stable associations with liver cancer in our study. Previous studies have also reported relatively consistent associations between pollutants exposure and liver cancer. We therefore suggest using morbidity outcomes in future studies to further delineate the associations between air pollution and colorectal / liver cancer. However, given that it is difficult to detect early-stage stomach cancer and the 5-year survival rate of stomach cancer is moderately high (38.6%) in Taiwan (Allemani et al., 2018), stomach cancer mortality may not approximate morbidity. We speculate that this might explain why no associations were observed. Also, we could not exclude the possibility of no strong association between $PM_{2.5}$ and stomach cancer mortality due to the generally consistent findings in our and previous studies. Finally, residual confounding may exist due to unavailable detailed information on smoking volume. This may explain that we found a stronger association between $PM_{2.5}$ and gastrointestinal cancer mortality in smokers than non–/ever smokers. Further stratified analyses by smoking volumes are required. Missing information on gastrointestinal cancer related infectious diseases (such as Helicobacter pylori and Hepatitis) may also affect the association between $PM_{2.5}$ and gastrointestinal cancer mortality. Further studies are needed.

5. Conclusions

In conclusion, long-term exposure to ambient $PM_{2.5}$ was significantly associated with higher risk of deaths from gastrointestinal cancers and liver cancer. We also found an association between $PM_{2.5}$ and colorectal cancer mortality with marginal statistical significance. Strategies to strengthen air pollution control are necessary to prevent gastrointestinal cancer and reduce premature deaths.

Author statement

XQL and TCC conceptualized the study. LC, AKHL, TCC and XQL acquired the data resources and administrated the project. CG, YB and YCT performed data curation. CG is responsible for the formal analysis. CG, MCSW and XQL drafted the original manuscript. All authors critically reviewed and edited the manuscript. XQL acquired the funding. LC, AKHL, TT, TCC and XQL supervised this study.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2020.105640.

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