



BMJ Open Effect of ambient air pollution on the incidence of colorectal cancer among a diabetic population: a nationwide nested case-control study in Taiwan

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ABSTRACT

Objectives An increasing number of studies had shown that air pollution exposure may aggravate blood glucose control in patients with diabetes, an independent risk factor for colorectal cancer (CRC) proposed by some researchers. This study aimed to investigate the impact of exposure to ambient particulate matter with aerodynamic diameters $\leq 2.5 \mu\text{m}$ ($\text{PM}_{2.5}$) on the incidence of CRC among a diabetic population.

Design A nested case-control study.

Setting A subset data retrieved from the Taiwan's National Health Insurance Research Database.

Participants We identified patients with newly diagnosed diabetes ($n=1\,164\,962$) during 1999–2013. Participants who had subsequently developed an incident of CRC were placed into the case group, while controls were matched to the cases at a 4:1 ratio by age, gender, date of diabetes diagnosis and the index date of CRC diagnosis.

Methods and outcome measures All variables associated with the risk of CRC entered into a multinomial logistic regression model. The dose-response relationship between various average concentrations of $\text{PM}_{2.5}$ exposure and the incidence of CRC was estimated by logistic regression.

Results The study included a total of 7719 incident CRC cases matched with 30 876 controls of random sampling. The mean annual concentration of $\text{PM}_{2.5}$ was $35.3 \mu\text{g}/\text{m}^3$. After adjusting for potential confounders, a dose-response relationship was observed between the CRC risks and each interquartile increase of $\text{PM}_{2.5}$ concentration (Q1–Q2: 1.03 (0.95–1.11), Q2–Q3: 1.06 (0.98–1.15), \geq Q3: 1.19 (1.10–1.28) in model 2. The adjusted ORs (95% CI) of CRC incidence for each $10 \mu\text{g}/\text{m}^3$ increment of $\text{PM}_{2.5}$ was 1.08 (1.04–1.11). Moreover, a faster growing adapted Diabetes Complications Severity Index (aDCSI) score was noticed in CRC group compared with the controls, which also showed a significant association in our multivariate analysis (adjusted OR=1.28, 95% CI 1.18 to 1.38).

Conclusions Long-term exposure to high concentrations of $\text{PM}_{2.5}$ may contribute to an increased incidence of CRC among diabetic populations.

INTRODUCTION

Air pollution has been identified as the world's single largest environmental health

Strengths and limitations of this study

- This is a nested case-control study on a nationwide diabetic population in Taiwan over a 15-year follow-up period.
- We conducted two models of conditional logistic regression adjusting for demographic variables alone and with additional clinical variables, respectively.
- The adapted Diabetes Complications Severity Index score, reflecting long-term severity of diabetic complications, was used to assess the cumulative effects of air pollution on glycaemic control.
- Two-pollutant analysis in addition to $\text{PM}_{2.5}$ alone was employed to examine the joint effects of co-pollutants.
- There may be a misclassification bias because not all participants in the control group had been verified with colonoscopy.

risk by WHO and is estimated to have caused 4.2 million premature deaths worldwide in 2016 due to ischaemic heart disease and stroke. The International Agency for Research on Cancer classifies ambient particulate pollutants as a group 1 carcinogen related to lung cancer.¹ Robust evidence from both experimental and epidemiological studies has demonstrated that long-term exposure to air pollution (AP) such as particulate matter (PM), nitrogen dioxide (NO_2) and ozone (O_3) is a major risk factor for cardiovascular and cardiopulmonary disease and potentially cancer.^{2–5}

Some reports have linked PM with gastrointestinal diseases, including an increased risk of appendicitis,⁶ Crohn's disease in younger individuals⁷ and increased hospitalisation of patients with inflammatory bowel disease,⁸ implying an association between PM exposure and inflammatory diseases of the GI tract. However, there remains a lack of epidemiological evidence connecting exposure to

ambient air pollutants with the risk of colorectal cancer (CRC).^{9 10}

Patients with diabetes are reportedly a vulnerable group susceptible to both oncogenesis^{11–13} and the deleterious effects of AP.^{14 15} Documents accrued over the years suggest that diabetes is associated with an increased risk for several malignancies, such as cancer of the breast,¹⁶ pancreas¹⁷ and liver¹⁸ and may also increase the risk of all-cause mortality among people with cancer.¹³ In addition, diabetes has been suggested as an independent risk factor of CRC.¹⁹ A meta-analysis involving 15 studies concluded that individuals with diabetes mellitus (DM) had an 30% increased risk of CRC.²⁰ DM and CRC share similar risk factors, including physical inactivity, poor diet, excess alcohol consumption, obesity and cigarette smoking.^{21 22}

Fine particulate matter is adversely associated with metabolic syndrome-related outcomes such as type 2 diabetes mellitus (T2DM), insulin resistance, hypertension and obesity.^{23–25} Insulin resistance and associated hyperglycaemic, hyperinsulinaemia, oxidative stress and chronic inflammation are the potential mechanisms contributing to the development of diabetes-associated CRC.^{19 22 26} Hyperinsulinaemia mediates CRC development through insulin, a growth factor for both normal and cancerous colon cells, and insulin-like growth factor-1 (IGF-1), which may inhibit apoptosis, push forward the cell cycle and promote angiogenesis.^{27 28} Observational studies have demonstrated a linkage between elevated IGF levels and the risks of adenomatous polyps or CRC.^{29–31}

In Taiwan, we had an average PM_{2.5} concentration of 20.5 µg/m³ in 2017, higher than the WHO standard value.³² CRC has carried the highest incidence rate among all malignancies since 2007 for both genders combined and has contributed to the third most cancer-related deaths.³¹ Diabetes, with an estimated prevalence of approximately 11.46% among adult Taiwanese during 2013–2016, was ranked as the fifth leading cause of all deaths.³² Both diseases affect a growing proportion of the general population and bring a heavy burden to the healthcare system in Taiwan.

To explore the role of AP exposure in the risks of diabetes-related malignancies, we conducted the epidemiological study that focus on whether long-term exposure to higher levels of ambient PM_{2.5} may impair glucose metabolism and therefore influence the incidence of CRC in the diabetic population.

METHOD

Data source

The dataset stem from the Taiwanese National Health Insurance Research Database (NHIRD). The NHI programme, implemented on 1 March 1995, provides compulsory universal health insurance, which covers all forms of healthcare services for 98% of the island's population. We retrieved admission and outpatient records, including information on patient characteristics and up to five discharge diagnoses or three outpatient diagnoses

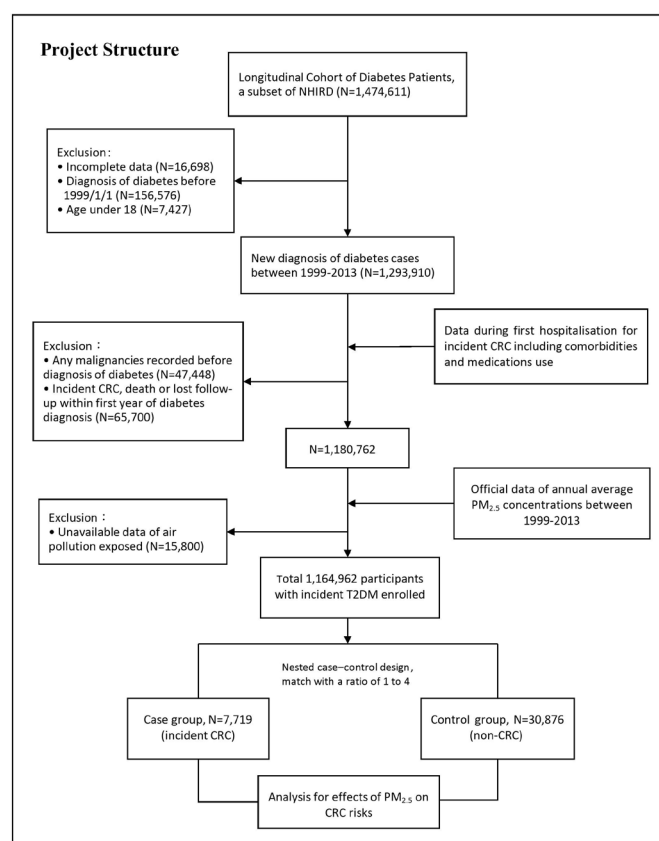


Figure 1 Study architecture and flow chart. CRC, colorectal cancer; NHIRD, National Health Insurance Research Database; T2DM, type 2 diabetes mellitus.

(the International Classification of Diseases, Ninth Revision (ICD-9)). The database had previously been used for epidemiological research and provided information regarding patient prescriptions, diagnoses and hospitalisations.^{33 34} Strict confidentiality guidelines were closely followed in accordance with personal electronic data protection regulations; the National Health Research Institute of Taiwan anonymises and maintains the NHI reimbursement data as files suitable for research.

Identification of study sample

In the study, we used a subset data from the NHIRD, the Longitudinal Cohort of Diabetes Patients, to identify adult patients with newly diagnosed T2DM (ICD-9 code 250 and A-code A181) during the follow-up period between 1 January 1999 and 31 December 2013. Subject enrolment was restricted to patients with diabetes diagnosis codes from at least one hospital admission or more than three outpatient visits within 1 year. We set up exclusion criteria for the T2DM cohort, including those with incomplete data, unavailable data of AP exposure, age under 18 years, diagnosis of diabetes before 1 January 1999 and previous medical records showing any malignancies before the diagnosis of diabetes (figure 1).

Case-control patient selection from the incident T2DM cohort

Within the T2DM cohort, patients who developed incident CRC (ICD-9-CM:153 and 154) during the follow-up

period were placed into the case group, with the date of CRC diagnosis established as the index date. Only patients who had been admitted with a diagnosis of CRC were enrolled in order to strengthen the validity. In consideration of potential reverse causality, patients who were diagnosed with CRC, dead or lost within the first year of diabetes diagnosis were excluded. Under the setting of a nested case-control study, subjects in the control group were identified through a random sampling at a ratio of 4:1 to the case group after matching for age, gender, date of T2DM diagnosis and the follow-up time or index date of CRC diagnosis.

Exposure assessment for residential PM_{2.5}

Hourly concentrations of ambient air pollutants including PM_{2.5}, particulate matter with aerodynamic diameters $\leq 10 \mu\text{m}$ (PM₁₀), sulfur dioxide (SO₂), nitric oxide (NO), NO₂, carbon monoxide (CO) and O₃ were measured at 76 monitoring stations, operated by the Taiwan Environmental Protection Administration (EPA) and located throughout the main Taiwan island. The official data of the annual average PM_{2.5} concentrations between 1999 and 2013 from the EPA was collected and sorted (see online supplemental file 1). Kriging, a method of spatial interpolation, was used to approximate the actual PM_{2.5} level at each participant's residential address using data from the nearest monitoring station. Kriging is a credible method that has been applied in previous studies for estimating ambient PM concentrations at residential addresses.^{35–38}

Potential confounders

All potentially confounding factors related to CRC were identified systematically between 1 January 1999 and the index date of CRC diagnosis. Confounders with sociodemographic characteristics such as age, gender, income and level of urbanisation were taken into consideration. Urbanisation levels in Taiwan are divided into four strata in Taiwanese National Health Research Institute publications; level I indicates the most urbanised communities, while level IV refers to the least urbanised communities.

Associated comorbidities, with a diagnosis validated by at least one hospital admission or more than three outpatient visits within 1 year, included Crohn's disease (ICD-9-CM: 555.0, 555.1, 555.2 and 555.9), ulcerative colitis (ICD-9-CM: 556), constipation (ICD-9-CM: 564.0), colon polyps (ICD-9-CM: 556.4, V12.72 and 211.3), hypertension (ICD-9-CM: 401–405), hyperlipidaemia (ICD-9-CM: 272.0, 272.1 and 272.4), atrial fibrillation (AF) (ICD-9-CM: 427.3 and 427.31), coronary atherosclerosis (ICD-9-CM: 412 and 414.0) and chronic kidney disease (ICD-9-CM: 585). As there were limited data available in the NHIRD regarding individual lifestyles, we used obesity (ICD-9-CM: 278.0), chronic obstructive pulmonary disease (ICD-9-CM: 496, 491.9 and 492.8) and alcohol-related disease (ICD-9-CM: 291, 303.0, 303.9, 535.3, 571.2 and 571.3) as surrogate variables for

overweight individuals, cigarette smokers and alcohol consumption levels, respectively.

Prescription medications that could potentially confound the association between diabetes and cancer risks were identified, including statins, antihyperlipidaemic drugs, antihypertensive drugs, antihyperglycaemic drugs, aspirin and non-steroidal anti-inflammatory drugs (NSAIDs).

Statistical analysis

Descriptive statistics regarding demographic and clinical characteristics were analysed to address the baseline distributions of age, gender, urbanisation levels, income, locations in Taiwan, underlying comorbidities, diabetes complications (adapted Diabetes Complications Severity Index (aDCSI) score) and medication use, as compared between the CRC and non-CRC groups. χ^2 test and t-test were used to analyse the differences among the categorical and continuous variables, respectively, between the two groups (table 1). The aDCSI score, representing the long-term severity of diabetes, had been validated with clinical outcomes.³⁹

Conditional logistic regression was conducted to estimate crude ORs and 95% CIs to assess the association between various PM_{2.5} concentrations divided by the interquartile range (IQR) and the risks of CRC incidence. Furthermore, we adjusted for demographic variables, including gender, age, income and urbanisation in model 1, and additionally adjusted for clinical variables such as comorbidities, drug use and changes in aDCSI score each year in model 2 (table 2).

We then performed the univariate and multivariate logistic regression models to assess the association between the occurrence of CRC and several potential risk factors, including exposure levels of PM_{2.5}, gender, age, income, urbanisation, comorbidities, drug use and change of aDCSI score each year (see online supplemental file 2).

Besides single-pollutant analysis of PM_{2.5}, as a continuous variable for each $10 \mu\text{g}/\text{m}^3$ increment in table 3, we evaluated the joint effects of each co-pollutant combined with PM_{2.5} in the two-pollutant model to test the consistency of dose-response relationship (table 3). The correlation coefficients of average concentrations between air pollutants were also estimated with the data provided in online supplemental file 3.

Sensitivity and subgroup analysis

In addition to the main analysis (model 1), sensitivity analyses were conducted by adding the presence of different comorbidities and drug use (table 4).

All the above analyses were conducted using the SAS V.9.4 software package. All p values were two tailed, and a p value <0.05 was considered significant.

Patient and public involvement

Patients or public were not involved in the research, including development of the research question, outcome

Table 1 The demographic and clinical characteristics between patients with and without CRC

Characteristic	Non-CRC CRC (n=7719) (n=30 876)		P value
	N(%)		
Follow-up period* (years)			
Mean (SD)	5.17 (2.84)	5.17 (2.84)	1
Gender			
Male	4145 (53.70)	16 580 (53.70)	1
Age (years)			
Mean (SD)	61.36 (10.69)	61.36 (10.68)	0.995
<35	62 (0.80)	245 (0.79)	
35–45	423 (5.48)	1683 (5.45)	
45–55	1722 (22.31)	6896 (22.33)	
55–65	2520 (32.65)	10 108 (32.74)	
65–75	2225 (28.82)	8909 (28.85)	
75–85	716 (9.28)	2836 (9.19)	
85≤	51 (0.66)	199 (0.64)	
Monthly income (NTD)			<0.004
0	3228 (41.82)	12 504 (40.50)	
1–15 840	1663 (21.54)	6368 (20.62)	
15 841–25 000	2196 (28.45)	9289 (30.08)	
≥25 000	632 (8.19)	2715 (8.79)	
Urbanisation level			0.430
Low	699 (9.06)	2968 (9.61)	
Moderate	1445 (18.72)	5798 (18.78)	
High	3439 (44.55)	13 741 (44.50)	
Very high	2136 (27.67)	8369 (27.11)	
Reign of Taiwan¶			<0.001
North	3134 (40.60)	12 957 (41.96)	
Central	1356 (17.57)	5836 (18.90)	
South	2 873 (37.22)	10 587 (34.29)	
East	356 (4.61)	1496 (4.85)	
Medical diseases			
Crohn's disease	110 (1.43)	316 (1.02)	0.003
Ulcerative colitis	36 (0.47)	68 (0.22)	0.002
Constipation	1803 (23.36)	5440 (17.62)	<0.001
Colon polyps	752 (9.74)	562 (1.82)	<0.001
Hyperlipidaemia	4230 (54.80)	17 138 (55.51)	0.264
Hypertension	5419 (70.20)	21 077 (68.26)	0.001
Obesity	122 (1.58)	488 (1.57)	0.291
Alcohol-related disease	295 (3.82)	804 (2.60)	<0.001
COPD	1157 (14.99)	4390 (14.22)	0.084
CKD	503 (6.52)	1521 (4.93)	<0.001
CAD	1427 (18.49)	5203 (16.85)	0.001
AF	354 (4.59)	1132 (3.67)	<0.001
Medications‡			
Statin	3107 (40.25)	12 548 (40.64)	0.534
Antihypertensive drugs‡	6302 (81.64)	24 391 (79.00)	<0.001
Antihyperglycaemic drugs‡	6088 (78.87)	22 942 (74.30)	<0.001

Continued

Table 1 Continued

Characteristic	Non-CRC		P value
	CRC (n=7719)	(n=30876)	
	N(%)		
Antihyperlipidaemic drugs‡	2024 (26.22)	8051 (26.08)	0.794
Aspirin	3628 (47.00)	14 501 (46.97)	0.955
NSAIDs	6924 (89.70)	27 616 (89.44)	0.507
aDCSI (score)			
^aDCSI/follow-time (mean (SD))§	0.21 (0.34)	0.17 (0.31)	<0.001
Onset (mean (SD))	0.87 (1.26)	0.89 (1.25)	0.316
End of follow-up (mean (SD))	1.88 (1.87)	1.73 (1.76)	<0.001

*The follow-time was defined from the start of the follow-up (the diabetes diagnostic date) to the end of the follow-up (the index date of the CRC in the case group to correspond with the control group).

†Drug use is defined as ≥28 cumulative defined daily doses (cDDDs) for taking.

‡Antihypertensive drugs (diuretics, beta-blockers, calcium channel blocker, ACEi and ARB); antihyperglycaemic drugs (insulins, biguanides, sulfonylureas, alpha-GI, thiazolidinedione and nglitidine); antihyperlipidaemic drugs (non-statin lipid-lowering drug, triglyceride-lowering drug).

§Wilcoxon rank-sum test. §T-test.

¶North (Keelung, Taipei, New Taipei, Taoyuan, Hsinchu and Miaoli); Central (Taichung, Changhua and Nantou); South (Yunlin, Chiayi, Tainan, Kaohsiung and Pingtung); and East (Yilan, Hualien and Taitung). ACEi, ACE inhibitor; aDCSI, adapted Diabetes Complications Severity Index; AF, atrial fibrillation; CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRC, colorectal cancer; NSAIDs, non-steroidal anti-inflammatory drugs; NTD, new Taiwan dollars.

measures, study design, recruitment and conduct of the study.

RESULTS

Among the incident T2DM cohort (n=1 164 962) during the follow-up period between 1999 and 2013, a total of 7719 patients with a recent diagnosis of CRC were identified in the case group. Under the nested case-control setting, a random sampling at a ratio of 4:1 to the case group was conducted, which obtained 30 876 subjects in the control group after matching by age, gender, date of T2DM diagnosis and follow-up time or index date of CRC diagnosis.

The baseline demographic and clinical characteristics are outlined in [table 1](#). Matching variables including age, gender and follow-up period were distributed evenly between the case and control patients. The mean follow-up period was 5.17 years. Male patients were dominant (53.70%) over females. The mean age at diagnosis was 61.36 years, with most cases falling into the age group of 55–65 years. Compared with the control group, the CRC case patients had prevalent comorbidities including Crohn's disease, ulcerative colitis, constipation, colon polyps, hypertension, alcohol-related disease, chronic kidney disease (CKD), coronary artery disease (CAD) and AF. The two groups displayed no differences in their

Table 2 The crude and adjusted ORs (95% CIs) of the exposure to PM_{2.5} and CRC in patients with diabetes mellitus

Variable	Case No. (%)	Control No. (%)	Total no.	Crude OR (95% CI)	Model1* aOR (95% CI)	Model2† aOR (95% CI)	P trend
≤Q1	1848 (23.94)	7811 (25.30)	9659	–	–	–	<0.001
Q1–Q2	1878 (24.33)	7770 (25.17)	9648	1.03 (0.96 to 1.11)	1.03 (0.96 to 1.14)	1.03 (0.95 to 1.11)	
Q2–Q3	1908 (24.72)	7731 (25.04)	9639	1.05 (0.98 to 1.13)	1.08 (1.00 to 1.16)	1.06 (0.98 to 1.15)	
≥Q3	2085 (27.01)	7564 (24.50)	9649	1.18 (1.09 to 1.27)	1.19 (1.10 to 1.29)	1.19 (1.10 to 1.28)	

*Model 1: adjusted for gender, age, income and urbanisation.

†Model 2: in addition to the variants of model 1, it also includes variables such as comorbidities, drug use and change of aDCSI score per year.

aDCSI, adapted Diabetes Complications Severity Index; aOR, adjusted OR; CRC, colorectal cancer; PM_{2.5}, particulate matter (diameter less than or equal to 2.5 µm).

aDCSI scores at onset, but a significantly increasing aDCSI score was observed in the case group (^aaDCSI/time: 0.21 vs 0.17, *p*<0.001), with a higher aDCSI score at the end of follow-up (1.88 vs 1.73, *p*<0.001).

Annual average concentrations of PM_{2.5} in Taiwan during the period of 1999–2013 are illustrated in figure 2, showing that the mean annual level of PM_{2.5} was 35.3 µg/m³, with the median level at 33.82 µg/m³ and an IQR of 11.41 µg/m³.

Table 2 lists the crude and adjusted ORs of CRC occurrence after exposure to PM_{2.5} of various concentrations. When divided into four groups determined by the distribution of PM_{2.5} concentrations (≤Q1: ≤29.49 µg/m³, Q1–Q2: 29.49–33.82 µg/m³, Q2–Q3: 33.82–40.90 µg/m³ and ≥Q3: ≥40.90 µg/m³), the crude OR (95% CI) comparing with the group ≤Q1 exhibit a dose–response relationship (Q1–Q2: 1.03 (0.96 to 1.11), Q2–Q3: 1.05 (0.98 to 1.13) and ≥Q3: 1.18 (1.09 to 1.27)). In both model 1 (adjusting for gender, age, income and urbanisation) and model

2 (adjusting for comorbidities, drug use and change of aDCSI score per year, in addition to the variables in model 1), the dose–response relationship of adjusted OR remained significant.

In multivariate analysis (model 2) shown in online supplemental file 2, multiple risk factors for CRC development, other than AP, show significant adjusted ORs (aORs) (95% CIs). These factors include urbanisation level, age: aOR 1.05 (0.99 to 1.12) per year, Crohn's disease: aOR 1.29 (1.03 to 1.61), ulcerative colitis: aOR 1.90 (1.24 to 2.89), constipation: aOR 1.37 (1.29 to 1.46), colon polyps: aOR 5.71 (5.08 to 6.41), alcohol-related disease: aOR 1.40 (1.21 to 1.62) and change of aDCSI score per year: aOR 1.28 (1.18 to 1.38). However, medications including statins, aspirin and NSAIDs among patients with diabetes seem to provide protective effects.

In a single-pollutant analysis, the adjusted ORs (95% CIs) of CRC occurrence for each 10 µg/m³ increment of PM_{2.5} level is 1.08 (1.04 to 1.11) in model 2. When combined with other pollutants in a two-pollutant analysis, the results appeared unaffected (table 3).

Sensitivity analysis yielded similar results regarding the dose–response relationship between the concentrations of PM_{2.5} exposure and the incidence of CRC under various additional covariates in model 1 (table 4).

Table 3 Adjusted ORs (95% CIs) for CRC by annual average pollutant concentrations: multiple-pollutant models with an increase of 10 µg/m³ in PM_{2.5}*

Pollutant	CRC incidence aOR† (95% CI)
Single-pollutant analysis	
PM _{2.5} ³ (per 10 µg/m ³)	1.08 (1.04 to 1.11)
Two-pollutant analysis	
PM _{2.5} with NO	1.07 (1.04 to 1.11)
PM _{2.5} with NO ₂	1.08 (1.04 to 1.11)
PM _{2.5} with NO _x	1.08 (1.04 to 1.11)
PM _{2.5} with CO	1.08 (1.04 to 1.11)
PM _{2.5} with SO ₂	1.07 (1.03 to 1.12)
PM _{2.5} with O ₃	1.08 (1.05 to 1.12)

*OR and 95% CIs were calculated on the basis of an increase of 10 µg/m³ in exposure to PM_{2.5}.

†Adjusted for gender, age, income, urbanisation, comorbidities, drug use and change of aDCSI score per year.

aDCSI, adapted Diabetes Complications Severity Index; aOR, adjusted OR; CRC, colorectal cancer; NO₂, nitrogen dioxide; PM_{2.5}, particulate matter (diameter less than or equal to 2.5 µm).

DISCUSSION

In this national-based, nested case–control study (ratio 1:4), we examined 7719 patients with incident CRC and 30876 random controls matched by age, gender, index date of CRC diagnosis and date of T2DM diagnosis among 1164962 patients with T2DM during the long follow-up period between 1999–2013. Our study observed the mean annual PM_{2.5} of 35.3 µg/m³ and the median level of 33.82 µg/m³, higher than threefold of the WHO standard, 10 µg/m³. When analysed with IQR of PM_{2.5} concentrations in table 2, a dose–response relationship between the incidents of CRC and ambient concentrations of PM_{2.5} exposure was observed with the crude OR (95% CI) of Q1–Q2: 1.03 (0.96 to 1.11), Q2–Q3: 1.05 (0.98 to 1.13), ≥Q3: 1.18 (1.09 to 1.27) compared with the

Table 4 Sensitivity analyses for the effects of PM_{2.5} exposure on the first-time CRC among diabetes mellitus patients in Taiwan with covariates

	≤Q1	Q1–Q2	Q2–Q3	≥Q3
	OR	OR (95% CI)	OR (95% CI)	OR (95% CI)
Main model*	1.0	1.03 (0.96 to 1.11)	1.08 (1.00 to 1.16)	1.19 (1.11 to 1.29)
Main model plus				
Medical diseases				
Crohn's disease	1.0	1.03 (0.96 to 1.11)	1.08 (1.00 to 1.16)	1.20 (1.11 to 1.29)
Ulcerative colitis	1.0	1.03 (0.96 to 1.12)	1.08 (1.00 to 1.16)	1.19 (1.11 to 1.29)
Constipation	1.0	1.03 (0.96 to 1.12)	1.07 (0.99 to 1.15)	1.19 (1.10 to 1.28)
Colon polyps	1.0	1.03 (0.96 to 1.11)	1.07 (0.99 to 1.16)	1.20 (1.11 to 1.29)
Hyperlipidaemia	1.0	1.03 (0.96 to 1.11)	1.07 (1.00 to 1.16)	1.19 (1.11 to 1.29)
Hypertension	1.0	1.03 (0.96 to 1.11)	1.08 (1.00 to 1.16)	1.20 (1.11 to 1.29)
Alcohol-related disease	1.0	1.03 (0.96 to 1.12)	1.08 (1.00 to 1.16)	1.20 (1.11 to 1.29)
Obesity	1.0	1.03 (0.96 to 1.11)	1.08 (1.00 to 1.16)	1.19 (1.11 to 1.29)
CKD	1.0	1.03 (0.96 to 1.11)	1.07 (0.99 to 1.16)	1.19 (1.11 to 1.28)
COPD	1.0	1.03 (0.96 to 1.12)	1.08 (1.00 to 1.16)	1.20 (1.11 to 1.29)
CAD	1.0	1.04 (0.96 to 1.12)	1.08 (1.00 to 1.16)	1.20 (1.12 to 1.29)
AF	1.0	1.03 (0.96 to 1.12)	1.08 (1.00 to 1.16)	1.20 (1.12 to 1.29)
Medication†				
Statin	1.0	1.03 (0.96 to 1.11)	1.08 (1.00 to 1.16)	1.19 (1.10 to 1.29)
Antihypertensive drugs	1.0	1.03 (0.96 to 1.11)	1.08 (1.00 to 1.16)	1.19 (1.11 to 1.29)
Diuretic	1.0	1.03 (0.96 to 1.11)	1.08 (1.00 to 1.16)	1.20 (1.11 to 1.29)
Beta-blocker	1.0	1.03 (0.96 to 1.11)	1.08 (1.00 to 1.16)	1.20 (1.11 to 1.29)
CCB	1.0	1.03 (0.96 to 1.11)	1.07 (1.00 to 1.16)	1.19 (1.11 to 1.28)
ACEi	1.0	1.03 (0.96 to 1.11)	1.08 (1.00 to 1.16)	1.19 (1.11 to 1.29)
ARB	1.0	1.03 (0.96 to 1.12)	1.08 (1.00 to 1.17)	1.20 (1.12 to 1.29)
Antihyperglycaemic drugs	1.0	1.03 (0.96 to 1.11)	1.07 (0.99 to 1.15)	1.18 (1.10 to 1.27)
Biguanide	1.0	1.03 (0.96 to 1.11)	1.08 (1.00 to 1.16)	1.19 (1.11 to 1.29)
Sulfonylurea	1.0	1.03 (0.96 to 1.11)	1.07 (0.99 to 1.16)	1.19 (1.10 to 1.29)
Alpha-GI	1.0	1.03 (0.96 to 1.11)	1.08 (1.00 to 1.16)	1.20 (1.12 to 1.29)
Thiazolidinedione	1.0	1.03 (0.96 to 1.11)	1.08 (1.00 to 1.16)	1.20 (1.11 to 1.29)
Meglitinide	1.0	1.03 (0.96 to 1.12)	1.08 (1.00 to 1.16)	1.20 (1.11 to 1.29)
Antihyperlipidaemic drugs	1.0	1.03 (0.96 to 1.11)	1.08 (1.00 to 1.16)	1.20 (1.11 to 1.29)
Non-statin lipid-lowering drug	1.0	1.03 (0.96 to 1.11)	1.08 (1.00 to 1.11)	1.20 (1.12 to 1.29)
Triglyceride-lowering drug	1.0	1.03 (0.96 to 1.11)	1.08 (1.00 to 1.16)	1.20 (1.11 to 1.29)
Aspirin	1.0	1.03 (0.96 to 1.11)	1.08 (1.00 to 1.16)	1.20 (1.11 to 1.29)
NSAIDs	1.0	1.03 (0.96 to 1.11)	1.08 (1.00 to 1.16)	1.19 (1.10 to 1.29)

*Models adjusted gender, age, income and urbanisation.

†Drug use is defined as ≥28 cumulative defined daily doses (cDDD) for taking.

ACEi, ACE inhibitor; AF, atrial fibrillation; Alpha-GI, alpha-glucosidase inhibitor; ARB, angiotensin II receptor blocker; CAD, coronary artery disease; CCB, calcium-channel blocker; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRC, colorectal cancer; NSAIDs, non-steroidal anti-inflammatory drugs; PM_{2.5}, particulate matter (diameter less than or equal to 2.5 µm).

group ≤Q1. After adjusting for potential confounders, the dose–response relationship remained robust in both model 1 and model 2. For each increase of 10 µg/m³ in PM_{2.5} concentration in table 3, the CRC risk increased by 8%. To the best of our knowledge, our study is the first research that investigates the AP effects on the incidence

of CRC in the Taiwanese diabetic population. There is scarce evidence in the literature to make a significant linkage between ambient AP exposure and the risk of CRC in general population, partly due to the long latency required from exposure to oncogenesis in most areas with relatively low concentrations of air pollutants. Our

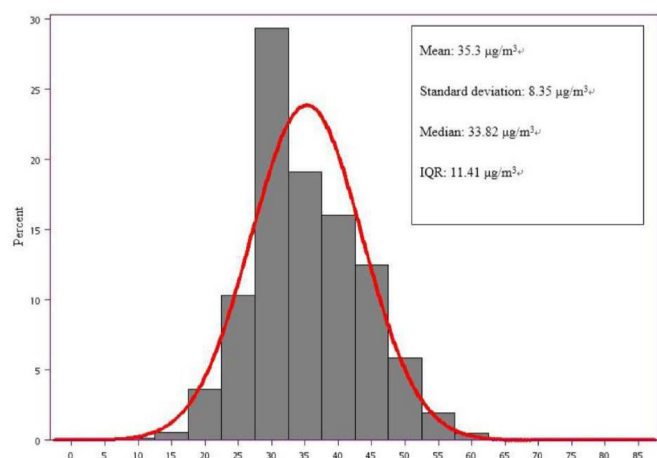


Figure 2 Annual average concentrations of $\text{PM}_{2.5}$ ($\mu\text{g}/\text{m}^3$) in Taiwan during 1999–2013. $\text{PM}_{2.5}$, particulate matter (diameter less than or equal to 2.5 μm).

results with statistical significance may benefit from the advantages of an extended follow-up period, detrimental high-level of AP concentrations and a large diabetic population, a group reportedly susceptible to both malignancies^{11–13} and AP.^{14 15}

The associations among the three entities, diabetes, AP and CRC, are complicated. Epidemiological studies had revealed the adverse impact of air pollutants on the risks of metabolic syndrome, along with its individual components of fasting blood glucose and hypertriglyceridaemia.^{40–42} Aside from DM incidence, some authors also found that AP may worsen blood glucose control and further aggravate diabetic complications. glycated haemoglobin (HbA1c) was one of the mostly used biomarkers to represent the status of sugar control. For example, a prospective analysis in Europe showed that an increase in HbA1c of 1% was associated with a 33% increase in CRC risks in multivariate models.⁴³ Another study suggested that $\text{PM}_{2.5}$ and NO_2 exposure were related to increased HbA1c levels, with a stronger association in diabetic than non-diabetic American participants,⁴⁴ which is consistent with the reported susceptibility of DM to AP.⁴⁵ In our study, the aDCSI score grew faster in the CRC group compared with non-CRC, which support the association between poor glycaemic control and the CRC risks. Nevertheless, few studies applied the aDCSI score as a measure of glycaemic status. The aDCSI scoring system was designed to quantify the severity of long-term diabetic complications, corresponding to our study objective of investigating the cumulative effects of AP on diabetic populations.^{46 47}

Other studies have elucidated the positive associations between AP exposure and insulin resistance. Brook *et al*⁴⁸ noted that subacute exposure to ambient $\text{PM}_{2.5}$, even at low levels for approximately 5 days, was associated with an increase in the homeostasis model assessment of insulin resistance (HOMA-IR), implying a reduction in insulin sensitivity. In a meta-analysis involving 35 studies, higher levels of fasting glucose, fasting insulin, the HOMA-IR,

HbA1c and C-peptide were all valid predictors for CRC risk.⁴⁹

There are both pathophysiological and molecular processes underlying the association between glucose metabolism and colorectal carcinogenesis. Insulin resistance, with its associated hyperglycaemic and hyperinsulinaemia, may induce colorectal carcinogenesis via inflammatory, oxidative stress and proliferative pathways.⁵⁰ Insulin possesses proproliferative properties and can reduce apoptosis while promoting the growth of CRC cell lines.⁵¹ Insulin or IGF-I signalling pathways either enhance proliferation, or inhibit apoptosis of colon epithelial cells, leading to carcinogenesis.^{28 52 53} In epidemiological studies, higher circulating concentrations of insulin, C-peptide and IGF-I have been demonstrated to increase the risk of CRC.^{30 54–59} Additionally, a significant increase in the risks of CRC with insulin therapy was also supported by growing evidence.⁶⁰

Experimental studies on diet-induced obese rats have shown subsequent insulin resistance, adiposity and visceral inflammation after $\text{PM}_{2.5}$ exposure.^{61–64} Inhaled small pollutant particles may penetrate the alveoli and enter systemic circulation⁶⁵ leading to low-grade chronic inflammation, as reflected by elevated systemic proinflammatory biomarkers.^{66–68} $\text{PM}_{2.5}$ -exposed mice demonstrated impaired insulin signalling through Akt in their skeletal muscles and adipose tissues.^{63 64} $\text{PM}_{2.5}$ exposure also triggers inflammation pathways mediated through JNK-AP1, NF- κ B and TLR4, while suppressing insulin receptor substrate 1-mediated insulin signalling through Akt and subsequent glycogen synthesis in the liver, which in turn leads to a non-alcoholic steatohepatitis-like phenotype with impaired hepatic glucose metabolism.⁶⁹

Significant differences in other variables were also observed between the two groups (table 1), including prevalence of comorbidities, deserving more discussions. A notably higher proportion of colon polyps exists among CRC subjects with undesirable sugar control reflected by rapidly raised aDCSI scores, in line with previous reports that poor glycaemic control in diabetes predicts higher tendency to develop colonic adenomatous polyps.^{70 71} Patients with inflammatory bowel disease are reportedly 2–6 times more likely to develop CRC than general population.^{72 73} Intestinal dysbiosis was well documented to have far-reaching effects on local immunity associated with the pathogenesis of inflammatory bowel disease and CRC and systemic diseases like obesity, diabetes and atherosclerosis.⁷⁴ As for constipation, a delayed stool transit time in patients with diabetes may alter the concentration of bile acids contributing to DNA damage and partly account for the incidence of CRC.⁷⁵ After a literary review, we found meta-analysis and cohort studies sharing the conclusion that patients with CKD have an increased risk of CRC compared with general population, matching with our results.^{76 77} Alcohol intake has been proposed to be associated with an increased risk of CRC, particularly remarkable with heavy drinking.^{78 79} A meta-analysis of 27 cohort and 34 case-control studies provide

evidence for a dose–response association between alcohol drinking and CRC risks, with stronger associations for heavy Asian drinkers.⁸⁰ Obesity might interact with alcohol on CRC risks. As reported by a Canadian study, alcohol consumption by people with a body mass index (BMI) <30 had an overall CRC OR of 0.8 (95% CI 0.60 to 1.10), whereas those drinking alcohol with a BMI >30, a group with prevailing hyperglycaemia similar to our cohort, had an overall CRC OR of 2.2 (95% CI 1.20 to 4.00, *p* trend<0.05).⁸¹ Central obesity and dyslipidaemia, components of metabolic syndrome in addition to hyperglycaemic and hypertension, were also linked with colorectal adenoma in some research.^{82–84} The reason for insignificant differences in coexisting hyperlipidaemia and obesity between our two groups is not well understood, most likely because of the increasing trend in the prescribing of statins and other lipid-lowering drugs for diabetic dyslipidaemia in Taiwan,^{85 86} while the statins had been found to provide a significant chemopreventive effect against colon cancer.^{87 88} AF and CAD also account for greater prevalence in the CRC group, presumably due to shared risk factors.

In two-pollutant analysis while PM_{2.5} combined with another pollutant except PM₁₀, the results appeared unaffected (table 3). Because only PM₁₀ among other co-pollutants showed high correlation with PM_{2.5} by estimating correlation coefficients, it was excluded for two-pollutant analysis to avoid multicollinearity. Some papers coincide with our finding of higher correlation between PM₁₀ and PM_{2.5}, as PM_{2.5} comprise major proportion of PM₁₀ fractions.⁸⁹ Compared with PM₁₀, smaller particles like PM_{2.5} may permeate lung alveoli and enter into the bloodstream, posing greater harm for systemic cardiovascular effects.⁹⁰ In addition, particulate matter has been shown to be stronger activators of innate immunity in comparison with gaseous pollutants.^{91 92}

A number of strengths in our study deserve to be mentioned. First, we analysed a total of 38 595 patients with diabetes for a prolonged follow-up period during 1999–2013, based on a nationally representative database, thus allowing for the results to be generalised for a large population. Second, apart from AP, we enrolled multiple variables including demographics, comorbidities, medications and changes in annual aDCSI score for adjusting in multivariate model to assess other confounding effects. Third, we applied the Kriging method, a spatial interpolation model, to obtain township-level estimates of PM_{2.5} levels that approximate to individual exposure. Fourth, we conducted two-pollutant analysis to evaluate if co-pollutants cause any influence, since other pollutants had reportedly been associated with insulin resistance and T2DM prevalence.^{42 93 94}

Nevertheless, several potential limitations should also be acknowledged. First, the NHIRD provides limited personal information regarding smoking habits, alcohol consumption, BMI, family history of T2DM or CRC, diet and physical activity. Thus, we used some comorbidities as surrogates to address those risk factors, such as COPD

for smoking, alcohol-related illness for alcohol consumption and obesity for high BMI. Second, similar to most epidemiological studies about AP exposure, residential exposure level may not fully reflect individual cumulative effects. Third, participants in the control group had not all been verified with colonoscopy, so potential odds of misclassification might exist.

CONCLUSION

Global data revealed that the highest prevalence of cardiometabolic conditions and most cardiovascular events are among developing countries.^{95 96} Nonetheless, even low levels of AP have been associated with an excess of cardiometabolic disorders.^{94 97} Our study suggests that long-term exposure to high PM_{2.5} concentrations may play a promoting role in the growing prevalence of diabetes, as well as an increased incidence of CRC among diabetic populations through the biological mechanisms of systemic inflammation, oxidative stress and elevated insulin resistance. In addition, undesirable control of blood sugar can increase the risk of CRC, as reflected by a raised aDCSI score in this article, warranting an earlier and intensive screening policy for CRC in this group. Considering the widespread prevalence of AP and diabetes, even modest contributions to malignancy risk could cause a substantial effect on public health. As with global urbanisation, ageing and overweight populations with sedentary lifestyles, the harmful influence of ambient AP on the metabolic epidemic might be underestimated and pose an enormous health burden deserving of more attention.

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