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Original Article

Is Long-term Ambient Air Pollutant Exposure a Risk Factor for Irritable Bowel Syndrome in Children? A 12-year Longitudinal Cohort Study

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Background/Aims
Recent studies suggest that air pollution may play a role in gastrointestinal disorders. However, the effect of long-term exposure to air pollution on childhood irritable bowel syndrome (IBS) is unclear. Hence, we conducted a nationwide cohort study to investigate the association between long-term air pollution exposure and the incidence and risk of IBS in Taiwanese children during 2000-2012.

Methods
We collected data from the Taiwan National Health Insurance Research Database, linked to the Taiwan Air Quality-Monitoring Database according to the insurant living area and the air quality-monitoring station locations. Children < 18 years old, identified from January 1st, 2000, were followed-up until IBS diagnosis or December 31st, 2012. The daily average air pollutant concentrations were categorized into 4 quartile-based groups (Q1-Q4). We measured the incidence rate, hazard ratios (HRs), and 95% confidence intervals for IBS stratified by the quartiles of air pollutant concentration.

Results
A total of 3537 children (1.39%) were diagnosed with IBS within the cohort during the follow-up period. The incidence rate for IBS increased from 0.84 to 1.76, from 0.73 to 1.68, from 0.85 to 1.98, and from 0.52 to 3.22 per 1000 person-years, with increase in the carbon monoxide, nitrogen dioxide, non-methane hydrocarbon, and methane quartile (from Q1 to Q4) exposure concentration, respectively. The adjusted HR for IBS increased with elevated carbon monoxide, nitrogen dioxide, non-methane hydrocarbon, and methane exposure in Q4 to 1.98, 2.14, 2.19, and 5.87, respectively, compared with Q1.

Conclusion
Long-term ambient air pollutant exposure is an environmental risk factor for childhood IBS.
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Key Words
Air pollutant; Child; Irritable bowel syndrome; Follow-up studies

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Introduction

Irritable bowel syndrome (IBS), which is the most common diagnosis in children with functional abdominal pain disorders, has become an important issue worldwide.[1] Childhood IBS may cause deterioration of children's quality of life, increase in medical costs, lower social and school performance, and increase the risk of subsequent psychiatric disorders.[2] The prevalence of pediatric IBS could be as high as 20% in some populations,[3,4] and up to 45% in some hospital-based populations.[5,6]

The pathogenesis of IBS is multifactorial, including visceral hypersensitivity, intestinal motility disturbance, intestinal inflammation, intestinal microbiome dysbiosis, food hypersensitivity, and psychological distress.[7] However, a number of pediatric IBS cases could not be explained by these mechanisms, and the causative factors of the symptoms are still not well understood.

Air pollution has become an increasingly important issue due to its adverse impact on public health. While classical studies of air pollution focused on respiratory and cardiovascular disorders,[8] recent studies suggested that air pollution may play a role in several gastrointestinal (GI) disorders, such as inflammatory bowel disease,[9] enterocolitis,[10] and functional abdominal pain.[11] Some evidence suggests inhalation of fine particles, or air pollution from coal industry, may disrupt the immune system and trigger gut inflammation by increasing gut permeability and altering gut microbiota.[9] The interplay between the gut microbiome and the immune system may influence the development of IBS.[4,7] Therefore, we investigated whether long-term ambient air pollutant exposure was an environmental risk factor for childhood IBS.

Materials and Methods

Data Source

The Taiwan National Health Insurance Research Database (NHIRD), an electronic claim database of the Taiwan National Health Insurance (NHI) program, covers 99% of the 25 million population of Taiwan and contracts with more than 90% of national health care facilities (https://nhird.nhri.org.tw/en/index.html).[12,13] The high reliability of the diagnostic data from the NHIRD has been evaluated in previous studies.[12,14] The NHIRD includes detailed information, such as outpatient visits, hospital admissions, prescriptions, procedures, and diagnosis of disease based on the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM).[14] Every individual in Taiwan has a unique personal identification number. The data on patient identities were scrambled cryptographically by the NHIRD to protect patient privacy.[12,14] All NHI datasets can be interlinked with the personal identification number of everyone. This study utilized a data file (the Children file) derived from the NHIRD, containing information from half of all insured children in Taiwan, chosen at random.[15] The dataset provided an adequate sample size to pursue the objectives addressed in this study. This study has been approved by the Institute Review Board of China Medical University Hospital (CRREC-103-048), and it complies with the principles outlined in the Declaration of Helsinki.

Study Population, Endpoints, Outcome of Interest, and Confounding Factors

This was a retrospective cohort study. We formed a child cohort by selecting individuals aged < 18 years in 2000-2012 and those who had diagnosed with IBS before were excluded. All individuals in this cohort were followed from baseline until either the first diagnosis of IBS, death, termination of insurance, or at the end of 31 December 2012. Individuals who had missing information such as their address, sex, and air pollution data were also excluded. The final study population contained 254 207 individuals. We identified individuals who received at least 2 consensus diagnoses of IBS (ICD-9-CM code 564.1) between 1 January 2000 and 31 December 2012 made by gastroenterologists. We defined newly diagnosed IBS as the first diagnosis of IBS. In this study, the mean follow-up years in IBS patients were 10.8 (SD, 2.84). The confounding factors were age, sex, monthly income, urbanization level of residence, number of consultations/visits with a physician per year, and allergy diseases. Allergy diseases were defined as having atopic dermatitis (ICD-9-CM code 691 or 691.8), allergic rhinitis (ICD-9-CM code 477) and/or asthma (ICD-9-CM code 493). The residential areas of the study subjects, which covered 365 Taiwan townships, were classified into seven levels of urbanization according to the method developed by Liu et al.[16] Level 1 was referring to the "most urbanized" and level 7 was referring to the "least urbanized" communities. The variables used in developing the township stratification for urbanization level consisted of the population density (people/km^2), population ratio of people with an educational level of college or above, population ratio of elder people over 65 years old, population ratio of agricultural workers, and the number of physicians per 100 000 people, among others.[16] As there were very small numbers of IBS cases at levels 4, 5, 6, and 7, these 4 levels were combined into a single group (Level 4). Therefore, the urbanization

level was stratified into four levels, from the highest density (Level 1) to the lowest density (Level 4). Monthly income was classified into 4 groups; < New Taiwan dollar (NT$)14 400, NT$14 400-18 300, NT$18 301-21 000, and > NT$21 000.

Exposure Measurement

The Taiwan Air Quality Monitoring Network (TAQMN) (http://taqm.epa.gov.tw/taqm/en/PsiMap.aspx) was established by the Taiwan Environmental Protection Administration (TEPA) in 1993 (http://www.epa.gov.tw/). TAQMN consists of 74 monitoring stations, which were fully automated and provided daily readings of air pollutants all over Taiwan. The Taiwan Air Quality-Monitoring Database (TAQMD) were released by the Taiwan Environmental Protection Agency, Executive Yuan during 1998-2012. The TAQMD contains the daily concentrations of carbon monoxide (CO), nitrogen dioxide (NO_2), non-methane hydrocarbon (NMHC), and methane (CH_4). The children file from NHIRD and TAQMD were linked according to the residential areas of insurants and the areas where the air quality-monitoring stations were located.[17] The residential area for each insured child was defined based on the sought treatment for common cold (acute nasopharyngitis: ICD-9-CM code 460). A daily average air pollutant concentration was calculated by dividing the cumulative daily air pollutant concentration by the duration from 2000 to the endpoint for each study participant. The daily average air pollutant concentrations were categorized into 4 groups based on quartiles, namely Q1, Q2, Q3, and Q4. CO was categorized as Q1 (< 0.56 parts per million [ppm]), Q2 (0.56-0.67 ppm), Q3 (0.68-0.81 ppm), and Q4 (> 0.81 ppm). NO_2 concentration was categorized as Q1 (< 18.3 parts per billion [ppb]), Q2 (18.3-23.6 ppb), Q3 (23.7-26.9 ppb), and Q4 (> 26.9 ppb). NMHC was categorized as Q1 (< 0.27 ppm), Q2 (0.27-0.34 ppm), Q3 (0.35-0.50 ppm), and Q4 (> 0.50 ppm). CH_4 was categorized as Q1 (< 2.01 ppm), Q2 (2.01-2.05 ppm), Q3 (2.06-2.11 ppm), and Q4 (> 2.11 ppm).

Statistical Methods

The sociodemographic factors in the current study included age, sex, monthly income, urbanization level of residential area, and daily average of exposure air pollutants. To test the distributed difference among daily average concentrations for each air pollutant by quartile and urbanization, chi-square test was used. The Kaplan–Meier method was used to estimate the cumulative incidence of IBS during the follow-up period among the different quartiles of each air pollutant. The incidence density rate of IBS (per 1000 person-years) was calculated by each quartile of daily average concentrations among the 4 air pollutants. Cox proportional hazard regression was used to estimate the hazard ratios (HRs) and 95% confidence interval (CIs) for IBS in Q2-Q4 level for air pollutant concentration compared the lowest one (Q1). Multivariable model was adjusted for age, sex, monthly income, urbanization level, number of consultations/visits with a physician per year, and allergy diseases. All analyses were performed using SAS 9.3 (SAS Institute Inc, Cary, NC, USA) and the Statistical Package for the Social Science (version 15.1; IBM Corp, Armonk, NY, USA). All statistical tests were considered statistically significant when 2-tailed *P*-values were < 0.05.

Results

A total of 3537 children (1.39%) were diagnosed with IBS

Table 1. Baseline Demographics and Exposure of Air Pollutants Exposure by Daily Average Concentration in Taiwan Children (N = 254 207)

Characteristics of study population	Values
Gender	
Boys	131 223 (51.6)
Girls	122 984 (48.4)
Age (yr)	6.43 ± 3.38
Urbanization level[a]	
1	84 679 (33.3)
2	81 371 (32.0)
3	48 142 (18.9)
4	40 015 (15.7)
Allergic diseases[b]	
No	220 682 (86.8)
Yes	33 525 (13.2)
Average number of consultations/visits with a physician per year	12.8 ± 7.96
Exposure of air pollutants (daily average)	
CO level (ppm)	0.79 ± 0.27
NO_2 level (ppb)	24.5 ± 5.58
NMHC level (ppm)	0.39 ± 0.17
CH_4 (ppm)	2.03 ± 0.13
Outcome	
Irritable bowel syndrome (yes)	3537 (1.39)
Follow-up periods (yr)	10.8 ± 2.84

[a]The urbanization level was categorized by the population density of the residential area into 4 levels, with level 1 as the most urbanized and level 4 as the least urbanized.
[b]Having any one of allergic diseases, including atopic dermatitis, allergic rhinitis, and asthma.
CO, carbon monoxide; NO_2, nitrogen dioxide; NMHC, non-methane hydrocarbon; CH_4, Methane; ppm, parts per million; ppb, parts per billion.
Values were expressed as n (%) or mean ± SD.

Table 2. Baseline Urbanization Level Among Quartiles of Daily Average Concentration of Air Pollutants in Taiwan Children (N = 254 207)

Air pollutant concentration	Urbanization level				*P*-value[a]
	1	2	3	4	
Carbon monoxide					< 0.001
Q1	4696 (14.6)	8961 (27.9)	6862 (21.3)	11 651 (36.2)	
Q2	12 575 (20.6)	25 469 (41.7)	11 668 (19.1)	11 409 (18.7)	
Q3	27 722 (35.4)	21 783 (27.8)	17 805 (22.7)	11 084 (14.1)	
Q4	39 686 (48.1)	25 158 (30.5)	11 807 (14.3)	5871 (7.1)	
Nitrogen dioxide					< 0.001
Q1	4765 (13.0)	11 919 (32.5)	5248 (14.3)	14 702 (40.1)	
Q2	13 605 (21.9)	20 584 (33.2)	14 101 (22.7)	13 764 (22.2)	
Q3	23 255 (32.3)	26 236 (36.5)	16 434 (22.8)	6060 (8.42)	
Q4	43 054 (51.5)	22 632 (27.1)	12 359 (14.87)	5489 (6.6)	
Non-methane hydrocarbon					< 0.001
Q1	10 790 (18.8)	16 860 (29.4)	9088 (15.8)	20 650 (36.0)	
Q2	20 824 (26.5)	27 181 (34.6)	19 826 (25.2)	10 732 (13.7)	
Q3	25 749 (46.7)	15 770 (28.6)	9423 (17.1)	4166 (7.56)	
Q4	27 316 (43.3)	21 560 (34.1)	9805 (15.5)	4467 (7.1)	
Methane					< 0.001
Q1	18 580 (30.6)	15 627 (25.7)	14 990 (24.7)	11 569 (19.0)	
Q2	20 819 (31.8)	23 461 (35.8)	11 941 (18.2)	9332 (14.2)	
Q3	24 684 (37.6)	22 754 (34.6)	10 649 (16.2)	7643 (11.6)	
Q4	20 596 (33.1)	19 529 (31.4)	10 562 (17.0)	11 471 (18.5)	

[a]Chi-square test.
Q, quartile.
The urbanization level was categorized by the population density of the residential area into 4 levels, with level 1 as the most urbanized and level 4 as the least urbanized. The daily average air pollutant concentrations were categorized into 4 groups based on quartiles for each air pollutant.
Values were expressed as n (%).

within the cohort of 254 207 children from January 1, 2001 to December 31, 2012. The sociodemographic factors of participants are demonstrated in Table 1. The mean age of the participants was 6.43 years (SD, 3.38). The proportion of boys and girls were similar (51.6% vs 48.4%). In the study population, there were more children living in higher population density areas (65.3%).

According to the location of the Taiwan air quality monitoring station, we collected the data of participants without IBS history under conditions of CO, NO_2, NMHC, and CH_4 exposure, respectively. We categorized the concentrations of each air pollutant into 4 levels based on quartiles, ranging from Q1 (the lowest concentration) to Q4 (the highest concentration). Children with highest exposure concentrations of CO, NO_2, NMHC, and CH_4 lived in areas with higher urbanization. In contrast, children with the lowest exposure concentrations of CO, NO_2, and NMHC lived in areas with the lowest urbanization (Table 2).

The incidence rate for IBS increased with CO, NO_2, NMHC, and CH_4 exposure concentration, increasing from 0.84 to 1.76, from 0.73 to1.68, from 0.85 to 1.98, from 0.52 to 3.22 per 1000 person-years, respectively (Table 3). The Kaplan–Meier plots (Figure) with pollutant concentration stratified by quartile showed that patients exposed to higher pollution concentrations had higher accumulative incidence of IBS than those exposed to lower pollution concentrations of CO, NO_2, NMHC, and CH_4. In the multivariable Cox proportional hazard regression, the adjusted HR (adjusted for age, sex, monthly income, and urbanization level) for IBS increased with the CO, NO_2, NMHC, and CH_4 exposure concentrations from 0.83 to 1.98, from 1.46 to 2.14, from 1.13 to 2.19, and from 1.37 to 5.87, respectively, compared with those exposed to the corresponding concentrations in Q1 level. When we also adjusted the number of consultations/visits with a physician per year, and allergy diseases, the adjusted HR for IBS were still increased with the CO, NO_2, NMHC, and CH_4 exposure level from 0.75 to 1.88, from 1.29 to 2.10, from 1.06 to 2.23, and from 1.45 to 6.02, respectively (Table 3).

We divided our cohort into 2 groups: children with and without allergic diseases. The incidence rate and adjusted HR for IBS were significantly increased with the CO, NO_2, NMHC, and CH_4

Table 3. The Risk of Irritable Bowel Syndrome in Children Exposed to Various Air Pollutants Stratified by Quartile of Daily Average Concentration in Cox Proportional Hazard Regression

Ambient air pollutants	IR	HR[a] (95% CI)	HR[b] (95% CI)
Carbon monoxide (ppm)			
Q1, < 0.56	0.84	Ref	Ref
Q2, 0.56-0.67	0.69	0.83 (0.72, 0.96)[c]	0.75 (0.65, 0.87)[d]
Q3, 0.68-0.81	1.51	1.74 (1.53, 1.97)[d]	1.51 (1.33, 1.72)[d]
Q4, > 0.81	1.76	1.98 (1.75, 2.26)[d]	1.88 (1.66, 2.14)[d]
Nitrogen dioxide (ppb)			
Q1, < 18.3	0.73	Ref	Ref
Q2, 18.3-23.6	1.11	1.46 (1.28, 1.67)[d]	1.29 (1.13, 1.48)[d]
Q3, 23.7-26.9	1.31	1.70 (1.50, 1.94)[d]	1.55 (1.36, 1.77)[d]
Q4, > 26.9	1.68	2.14 (1.88, 2.43)[d]	2.10 (1.85, 2.39)[d]
Non-methane hydrocarbon (ppm)			
Q1, < 0.27	0.85	Ref	Ref
Q2, 0.27-0.34	0.96	1.13 (1.01, 1.26)[c]	1.06 (0.95, 1.18)
Q3, 0.35-0.50	1.52	1.69 (1.51, 1.89)[d]	1.58 (1.41, 1.76)[d]
Q4, > 0.50	1.98	2.19 (1.97, 2.43)[d]	2.23 (2.01, 2.47)[d]
Methane (ppm)			
Q1, < 2.01	0.52	Ref	Ref
Q2, 2.01-2.05	0.73	1.37 (1.20, 1.56)[d]	1.45 (1.27, 1.65)[d]
Q3, 2.06-2.11	1.14	2.09 (1.85, 2.36)[d]	2.17 (1.91, 2.45)[d]
Q4, > 2.11	3.22	5.87 (5.24, 6.58)[d]	6.02 (5.37, 6.75)[d]

[a]HR, adjusted for age, sex, monthly income, and urbanization level.
[b]HR, adjusted for age, sex, monthly income, urbanization level, number of consultations/visits with a physician per year, and allergy diseases (atopic dermatitis, allergic rhinitis, and asthma).
[c]$P < 0.01$, [d]$P < 0.001$.
IR, incidence rate (per 1000 person-years); HR, hazard ratio; CI, confidence interval; Q, quartile; ppm, parts per million; ppb, parts per billion; Ref, reference group.
The daily average air pollutant concentrations were categorized into 4 groups based on quartiles for each air pollutant.

exposure concentrations in both groups (Supplementary Table 1). Baseline characteristics of participants exposed to each ambient air pollutant was listed in supplementary Tables 2-8. Comparisons of differences of incidences and associated hazard ratios for IBS in participants exposed various concentrations of air pollutants were listed in supplementary Table 9.

Discussion

Air pollution has become the greatest worldwide environmental health risk.[8] Air pollution is a mixture of multiple substances including gaseous pollutants such as CO, NO_2, ozone, volatile organic compounds, and particulate matter (PM).[18] Our results indicate that individuals that live in more urbanized areas had higher air pollutant (CO, NO_2, NMHC, and CH_4) exposure, most likely due to the density of the vehicles and population being high in urban areas. Hence, the consumption of large amounts of energy and resources results in the emission of large amounts of air pollutants into the atmosphere in urban settings.

Air pollutants directly affect the respiratory system and cause pulmonary disorders such as asthma exacerbation.[8] However, it is also associated with non-pulmonary diseases, including stroke,[19] rheumatoid arthritis,[16] and increased mortality of colon cancer patients.[20] These findings implied that air pollutants do not only affect the respiratory system directly, but are also related to systemic inflammation.

A human study showed that air pollutants could enter the intestine directly through consumption of contaminated food and water.[21] A previous study has demonstrated that more than 10^{12} microparticles were ingested per person daily in the western world.[22] In addition, the inhaled particles were removed from the airway through mucociliary clearance, and then, swallowed in the GI tract.[23]

Animal studies have suggested that exposure to air pollutants causes intestinal cell damage, accompanied with intestinal inflammation. Dybdahl et al[24] showed that dietary exposure to diesels ex-

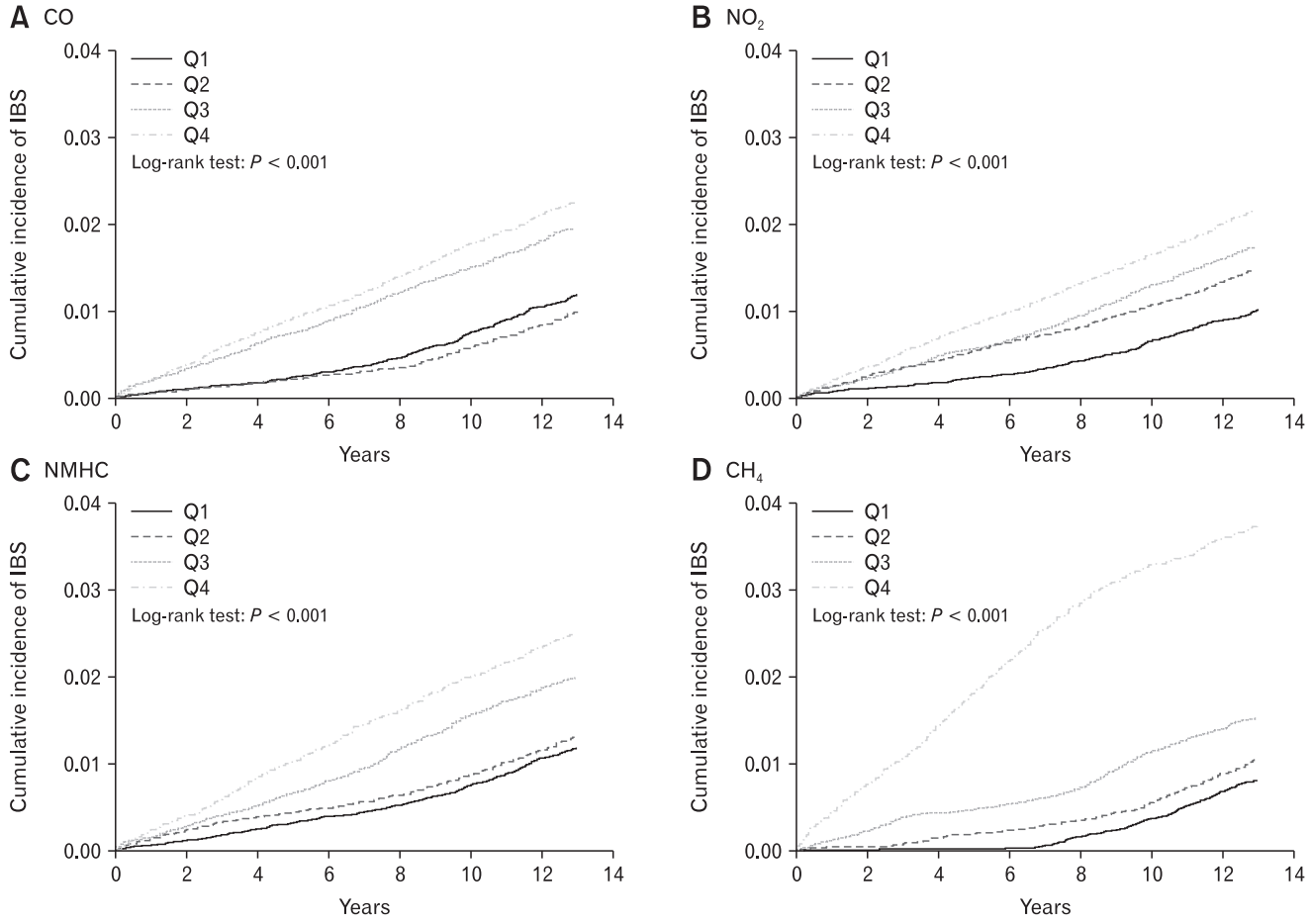

Figure. Kaplan-Meier curves of the accumulative incidence rate of irritable bowel syndrome (IBS) during the follow-up period among the different quartiles of each air pollutant. (A) Carbon monoxide (CO). (B) Nitrogen dioxide (NO_2). (C) Non-methane hydrocarbon (NMHC). (D) Methane (CH_4).

haust particles in rats, even in relatively low levels can cause DNA adducts and oxidative stress, results in DNA strand breaks, and apoptosis in colon mucosa. Kish et al[25] found that GI exposure to PM in mice increased pro-inflammatory cytokine in both small and large intestine, and increased gut permeability. Mutlu et al[26] also noted that GI exposure to high doses of PM in mice caused intestinal epithelial cell death, disruption of tight junction, increased gut permeability, and induced gut inflammation. These findings were compatible with human studies which demonstrated an impaired intestinal epithelial barrier and an increased intestinal permeability, with accompanying low-grade gut inflammation in patients with IBS.[27,28]

The association between IBS and gut microbiome has been well established.[29] Several animal studies have indicated that ingested air pollutants alter the gut microbiome. Kish et al[25] showed that ingestion of PM in mice alters short chain fatty acid concentration in the colon and changed the percentage of Verrucomicrobia, Bacteroidetes, and Firmicutes. Salim et al[30] demonstrated that *Bifidobacterium* was decreased in interleukin-10-deficient mice fed with PM. In addition, increased colonic pro-inflammatory cytokines, bacterial translocation into mesenteric lymph nodes, and increased serum lipopolysaccharide were also observed in those mice.

Furthermore, animal studies have also indicated the association between air pollution and GI motility. Roth and Tansy[31] demonstrated that high concentration of gaseous air pollutants, including CO, NO_2, and ozone caused gastric contractility impairment in rats. Kaplan et al[11] demonstrated that GI exposure to PM impaired colonic contractility, and increased pain response in mice.

Our data provide strong evidence on the association between air pollution exposure and IBS in children. These data show that children exposed to higher air pollutant concentration had increased risk of IBS (Table 3). The correlation is still noted after adjustment

in monthly income, urbanization level, number of consultations/visits with a physician per year, and allergy diseases. The finding indicated that crowed or stressful environment, and frequency of doctor's visit for other diseases were not a confounding factor in our study. The risk of IBS in both children with and without allergic diseases are also similar (Supplementary Table 1). Although a previous study has suggested that children with allergic disease may have higher risk of IBS,[32] our data showed that the effect of air pollution in IBS was independent of allergic diseases.

The results are also consistent among various pollutants, although CH_4 exposure results in the highest adjusted HR for IBS, compared with other pollutants. Several studies have indicated the correlation between CH_4 and GI motility. CH_4 may slow down intestinal transit time,[33,34] augments small intestinal contractile activity,[34] and is associated with constipation-predominant IBS.[35] However, there is still lack of research focused on the association between other pollutants and IBS or other functional GI disorders.

Kaplan et al[11] have reported that the frequency of emergency department visits for non-specific abdominal pain in young individuals 15-24 years old was associated with the concentration of air pollutants. To the best of our knowledge, our study is the first one to suggest the correlation between air pollution and IBS in children. There are several strengths in this study. First, our cohort is a national-based cohort, with a large sample size and long-term follow-up. Moreover, the IBS diagnosis was determined by a physician and not using self-reported questionnaires completed by patients or their parents.

On the other hand, potential limitations that could serve as confounders to this study should be acknowledged. First, genetic and behavioral factors, severity and subtype of IBS were not captured in administrative claims databases. Second, children with higher exposure of air pollution lived in areas with higher urbanization. Children living in more crowded environment might have higher stress associated with more crowded housing. Moreover, children in more polluted areas may have more non-GI diseases and consultations for respiratory tract infections and allergic diseases. The more frequent that a child consults the doctor has more opportunities of being diagnosed with IBS. Thus, we had adjusted for possible confounders. Even though we adjusted for these variables statistically, the bias cannot be eliminated thoroughly. Such limitation is inevitable in an observational study. Third, coding accuracy and financial incentives may lead to bias when using ICD-9 codes for diagnosis in large insurance claims data for research. Fourth, data from fixed monitoring stations may not reflect the true exposure level to air pollutants in patients. Fifth, some studies[36,37] had noted less consultation for pediatric functional abdominal pain disorders during the summer. However, in this study design, we used the daily average air pollutant concentrations, and seasonal variation of air pollutant concentration was not found. Previous study showed that the prevalence of IBS in children was ranges from 2.8% to 14%.[38,39] The prevalence varies because considerable heterogeneity exists between studies in methodology, study population and the use of different diagnostic criteria to define IBS. However, all these data are prevalence, not the incidence of IBS. Our data showed the incidence rate for IBS increased with CO, NO_2, NMHC, and CH_4 exposure concentration, increasing from 0.84 to 1.76, from 0.73 to1.68, from 0.85 to 1.98, from 0.52 to 3.22 per 1000 person-years, respectively.

In conclusion, our study is the first study to demonstrate that long-term exposure to ambient air pollutants is a potential risk factor for childhood IBS. Exposure to high level of gaseous air pollutants (CO, NO_2, NMHC, and CH_4), especially CH_4, is significantly associated with the development of childhood IBS. Our results suggest the effects of air pollution on GI diseases, but further investigation on this issue is still needed.

Supplementary Materials

Note: To access the supplementary tables mentioned in this article, visit the online version of *Journal of Neurogastroenterology and Motility* at http://www.jnmjournal.org/, and at https://doi.org/10.5056/jnm18135.

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Conflicts of interest: None.

Author contributions: Miguel Saps and Chang-Ching Wei conceptualized and designed the study, coordinated and supervised data collection, critically reviewed the manuscript, and approved the final manuscript as submitted; Teck-King Tan drafted the initial manuscript; and Cheng-Li Lin carried out the analysis, reviewed and approved the final manuscript as submitted.

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