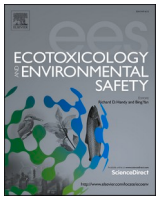
Ecotoxicology and Environmental Safety 275 (2024) 116245

Contents lists available at ScienceDirect

Ecotoxicology and Environmental Safety

journal homepage: www.elsevier.com/locate/ecoenv



Chronic exposure to ambient air pollution and the risk of non-alcoholic fatty liver disease: A cross-sectional study in Taiwan and Hong Kong

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ARTICLE INFO

Edited by Dr. Renjie Chen

Key words:
Fine particulate matter
Nitrogen dioxide
Ozone
Non-alcoholic fatty liver disease
Advanced fibrosis

ABSTRACT

Background: Information on the relation of air pollution with non-alcoholic fatty liver disease (NAFLD) is scarce. We thus conducted a large cross-sectional study in Asia to investigate the role of air pollution in NAFLD.
Methods: We recruited 329,048 adults (mean age: 41.0 years) without other liver disease (hepatitis and cirrhosis) or excessive alcohol consumption in Taiwan and Hong Kong from 2001 to 2018. The concentrations of nitrogen dioxide (NO_2) and ozone (O_3) were estimated using a space–time regression model, and the concentrations of fine particulate matter ($PM_{2.5}$) was evaluated using a satellite-based spatio-temporal model. NAFLD was determined using either the fatty liver index (FLI) or the hepatic steatosis index (HSI). The NAFLD-related advanced fibrosis was defined according to BARD score or the fibrosis-4 (FIB-4). A logistic regression model was adopted to explore the relationships of ambient air pollution with the odds of NAFLD and NAFLD-related advanced fibrosis.
Results: We found positive relationships between $PM_{2.5}$ and the odds of NAFLD and advanced fibrosis, with every standard deviation (SD, 7.5 μg/m^3) increases in $PM_{2.5}$ exposure being associated with a 10% (95% confidence interval [CI]: 9%–11%) increment in the prevalence of NAFLD and an 8% (95% CI: 7%–9%) increment in the prevalence of advanced fibrosis. Similarly, the prevalence of NAFLD and advanced fibrosis increased by 8% (95% CI: 7%–9%) and 7% (95% CI: 6%–8%) with per SD (18.9 μg/m^3) increasement in NO_2 concentration, respectively. Additionally, for every SD (9.9 μg/m^3) increasement in O_3 concentration, the prevalence of NAFLD and advanced fibrosis decreased by 12% (95% CI: 11%–13%) and 11% (95% CI: 9%–12%), respectively.
Conclusion: Higher ambient $PM_{2.5}$ and NO_2 are linked with higher odds of NAFLD and advanced fibrosis. Our findings indicate that reducing $PM_{2.5}$ and NO_2 concentrations may be an effective way for preventing NAFLD. Further studies on O_3 are warranted.

1. Introduction

In addition to causing chronic liver disease, non-alcoholic fatty liver disease (NAFLD) has been considered as a significant indicator of liver transplant need.(Pais et al., 2016) The Global Burden of Disease Study, (2019) estimates that NAFLD is responsible for approximately 4.42 million [95% confidence interval (CI) 3.35–5.67] disability-adjusted life years (DALYs) (GBD, 2019 Diseases and Injuries Collaborators, 2020). In the past decade, NAFLD has been recognized as a key contributor for liver-related morbidity and mortality, as well as a multisystem condition that affects extrahepatic organs, such as chronic kidney disease (CKD), (Musso et al., 2014) cardiovascular disease (CVD), (Targher et al., 2016) telomere length (Wu et al., 2023), and type 2 diabetes. (Mantovani et al., 2018) No pharmacological treatment has yet been approved to manage NAFLD and advanced fibrosis, and lifestyle changes such as the alteration of diet and physical activity have thus been recognised as the fundamental measures to control NAFLD and development of its complications.

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https://doi.org/10.1016/j.ecoenv.2024.116245
Received 25 November 2023; Received in revised form 17 March 2024; Accepted 18 March 2024
Available online 22 March 2024

In addition to the modifiable lifestyle factors, environmental factors are also considered as important contributors to the burden of NAFLD. Air pollution is globally ubiquitous and has been identified as one of the top environmental contributors to the global disease burden. For example, the Global Burden of Disease 2019 Risk Factors Collaborators revealed that air pollution caused 6.67 million deaths globally that year. (GBD, 2019 Diseases and Injuries Collaborators, 2020). Animal studies suggested that inhaled air pollutants can promote the progression of NAFLD (Wang et al., 2019 Xu et al., 2019) Limited epidemiological literature have also evaluated the relationships of chronic exposure to air pollution with metabolic dysfunction-associated fatty liver disease (MAFLD), (Guo et al., 2022) liver enzymes, (Hsieh et al., 2018; Kim et al., 2019; Markevych et al., 2013; Zhang et al., 2019) hepatic steatosis, (Li et al., 2017) and liver cancer, (Pan et al., 2016; So et al., 2021) and the results are inconsistent. However, information on its association with NAFLD is scarce. To the best of our knowledge, only a few epidemiologic studies have examined the health effect of air pollutants on NAFLD in mainland China (Deng et al., 2023), Germany (Matthiessen et al., 2023), and UK (Li et al., 2023). There is a need to examine the associations in different populations and regions with different air pollution levels. Furthermore, associations of air pollution with NAFLD-related advanced fibrosis remain unclear. Accordingly, we conducted this study to investigate the associations of long-term exposure to $PM_{2.5}$, nitrogen dioxide (NO2) and Ozone (O3) with the risk of NAFLD and NAFLD-related advanced fibrosis in 329,048 Taiwan and Hong Kong residents. By including participants from two regions with a wider range of air pollution concentrations, our study not only validates the associations reported by previous research but also enhances the generalizability of these findings beyond the limitations of studies focused on a single area.

2. Methods

2.1. Study population

The participants in this study were sourced from two active, evolving cohorts in Taiwan and Hong Kong, which were initiated by the MJ Health Management Institution. Our prior work has detailed the Taiwan cohort extensively (Guo et al., 2018; Zhang et al., 2017; Zhang et al., 2018; MJ Health Research Foundation, 2016) Since 1994, this private, subscription-based institution has been providing exhaustive health screening services to the Taiwanese populace. Members are advised to undergo annual health screenings, which encompass a range of examinations including blood and urine tests, medical imaging, body measurement evaluations, and lung function tests. Additionally, at each appointment, participants complete a standardized questionnaire designed to collect information on their sociodemographic profiles, lifestyle choices, and health history. This information has been systematically digitized beginning in 1996, resulting in the enrollment of over 600,000 individuals into the Taiwan cohort from 1996 to 2016.

In 2002, the medical screening initiative was introduced to Hong Kong, where the Hong Kong MJ cohort followed the same protocols and medical evaluation items as its counterpart. Between 2002 and 2018, around 61,000 inhabitants of Hong Kong enrolled in the programme. Participants from both cohorts provided their consent for the use of data obtained from their medical screenings exclusively for research purposes by signing a consent form. The conduct of this study received ethical clearance from the Joint Chinese University of Hong Kong–New Territories East Cluster Clinical Research Ethics Committee (2018.388).

Figure S1 illustrates the selection process of the participants. Within the Taiwan MJ cohort, 439,836 individuals aged 20 years and above were incorporated from 2001 to 2016, coinciding with the availability of $PM_{2.5}$ measurements. A total of 2957 adults were subsequently removed from the analysis due to incomplete air pollution data, and another 65,026 were omitted because of missing covariate data or variables relevant to the estimation of NAFLD. These variables included demographic details (n = 20,963), lifestyle factors (n = 29,327), liver enzyme levels (n = 14,661), as well as measurements of blood pressure, fasting glucose, triglycerides, and blood platelets (n = 75). Additionally, 65,003 participants were disqualified due to neither defined as presence or absence of NAFLD (n=25,443), high alcohol intake (defined as ≥7 drinks per week, n = 7444), or self-reported physician-diagnosed liver disease, such as hepatitis and cirrhosis (n = 32,116).

The Hong Kong MJ cohort enlisted 60,041 adults aged 20 and over between 2002 and 2018. From this group, a total of 22,545 were not included in the study due to incomplete air pollution data, while 11,845 were omitted owing to absent information on covariates or variables needed for NAFLD estimation. The missing data spanned demographic information (n = 4227), lifestyle habits (n = 6374), liver function tests (n = 1235), as well as readings for blood pressure, fasting glucose, triglycerides, and blood platelets (n = 9). Additionally, 3453 participants were disqualified due to neither defined as presence or absence of NAFLD (n=1700), engaging in heavy drinking (defined as ≥7 drinks per week, n = 470), or having a self-reported physician-diagnosed liver ailment such as hepatitis or cirrhosis (n = 1283).

A total of 329,048 participants without other liver conditions (hepatitis and cirrhosis) or a history of heavy alcohol use (comprising 306,850 from the Taiwan MJ cohort and 22,198 from the Hong Kong MJ cohort) were considered for analyzing the association between ambient $PM_{2.5}$ exposure and NAFLD, as well as NAFLD-related fibrosis. Within this group, 111,800 individuals were not included in the study examining the effects of NO_2 and ozone O_3 due to either their registration prior to 2005 (n=110,953), which predates the availability of NO_2 and O_3 assessments, or due to incomplete data on NO_2 or O_3 levels (n = 919). Consequently, 217,176 adults were incorporated into the evaluation of the relationship between ambient NO_2/O_3 exposure and NAFLD, including NAFLD-related fibrosis. Compared with the adults excluded due to incomplete information on $PM_{2.5}$ or covariates, the participants included were more educated, less likely to being smoking and drinking, more likely to take physical activity. They also had higher level of γ-glutamyl transferase. What's more, compared with participants from Taiwan, those in Hong Kong were generally older, less educated and less likely to be smokers. The participants in Hong Kong were also less likely participate in physical activity and consume vegetable, and exposed to higher levels of $PM_{2.5}$, NO_2, and lower levels of O_3.

2.2. Outcome ascertainment

The primary outcomes examined were the presence of NAFLD and advanced fibrosis associated with NAFLD. Blood samples from the participants were collected following an overnight fast. A biochemical autoanalyzer was employed to assess the concentrations of three hepatic enzymes (γ-glutamyl transferase [GGT], alanine aminotransferase [ALT], and aspartate aminotransferase [AST]), along with triglycerides, glucose, and blood platelets (from 2001 to 2004 using Hitachi 7150, Tokyo, Japan; and from 2005 to 2016 using Toshiba C8000, Tokyo, Japan). Additionally, waist circumference (WC) was measured at the broadest area of the abdomen (Yu et al., 2021).

The fatty liver index (FLI) and hepatic steatosis index (HSI) were adopted to define NAFLD. These indexes have been externally validated and used in previous epidemiological studies (Bedogni et al., 2006; Hajifathalian et al., 2019; Kim et al., 2020; Lee et al., 2010; Meffert et al., 2014). The HSI was calculated using the following equation:

$$HSI = 8 \times (ALT/AST) + BMI + (2 for female; + 2 for diabetes)$$

where ALT and AST are in U/L and BMI is in kg/m^2. Participants with HSI < 30 (sensitivity = 93.1%) and HSI > 36 (specificity = 92.4%) were considered as absence and presence of fatty liver, respectively. Participants with HSI of 30–36 were considered as neither presence nor absence of fatty liver. The HSI has been reported to have an accuracy of 0.812 (95% CI, 0.801–0.824) (Lee et al., 2010).

The FLI was calculated based on the following equation:

$$FLI = \frac{e^{0.953\times\ln(\text{triglycerides})+0.139\times BMI+0.718\times\ln(GGT)+0.053\times\text{waist circumference}-15.745}}{1+e^{0.953\times\ln(\text{triglycerides})+0.139\times BMI+0.718\times\ln(GGT)+0.053\times\text{waust circumference}-15.745}}\times 100$$

where triglycerides is in mg/dL, BMI is in kg/m^2, GGT is in U/L and waist circumference is in cm. Participants with FLI $\geq$ 60 (specificity = 86%) were considered as presence of fatty liver, whereas those with FLI $<$ 30 (sensitivity = 87%) were considered as absences of fatty liver. Participants with FLI of 30–60 were considered as neither presence nor absence of fatty liver. The FLI also had a good diagnostic accuracy of 0.84 (95% CI 0.81–0.87). (Bedogni et al., 2006) We defined the presence of NAFLD as HSI $>$ 36 or FLI $\geq$ 60 and the absence of NAFLD as HSI $<$ 30 and FLI $<$ 30.

For NAFLD-related advanced fibrosis, we used Fibrosis-4 (FIB-4) and the BARD score.(Harrison et al., 2008 Shah et al., 2009; Wu et al., 2021a); FIB-4 was calculated by the means of the following equation:

$$\text{FIB}-4 = (\text{Age}\times\text{AST})\Big/(\text{Platelets}\times\sqrt{\text{ALT}})$$

where ALT and AST are in U/L and platelets are in $\times 10^9$/L. Individuals were classified into three groups according to FIB-4: low (FIB-4 $<$ 1.30), intermediate (FIB-4: 1.30–2.67) and high probability for advanced fibrosis (FIB-4 $>$ 2.67) (Shah et al., 2009).

The BARD score was calculated based on BMI ($\geq$ 28 kg/m^2 = 1 point), AST-to-ALT ratio ($\geq$ 0.8 = 2 points) and type 2 diabetes (1 point) (Ampuero et al., 2020). Individuals with a BARD score of 0–1 were classed to a low probability group for advanced fibrosis, and those with scores of 2–4 were classed to a high probability group for advanced fibrosis.

NAFLD individuals with a FIB-4 $>$ 2.67 or a BARD score of 2–4 were diagnosed as having NAFLD-related advanced fibrosis.

2.3. Assessment of ambient air pollution

$PM_{2.5}$ levels at ground level on a 1 km by 1 km grid were assessed using a spatio-temporal model based on satellite data (Guo et al., 2018; Lin et al., 2015; Zhang et al., 2017). Aerosol optical depth (AOD) data, essential for predicting ground-level $PM_{2.5}$, were supplied by U.S. NASA satellites. This model's accuracy was corroborated by comparing its data with readings from 565 stations in Mainland China, Hong Kong and Taiwan, revealing correlation coefficients ranging from 0.79 to 0.83 with the annual average $PM_{2.5}$ levels recorded at these stations (Zhang et al., 2017).

The geographical and temporal weighted regression (GTWR) was utilized to estimate NO_2 and O_3 levels (Wu et al., 2021c). This statistical model, refined through satellite remote sensing and surface meteorological data, boasts a spatial resolution of 1 km$\times$1 km and has demonstrated daily correlations of 0.76 (Wu et al., 2021b). The GTWR model employs a weighting scheme that accounts for both spatial and temporal factors, allowing for the consideration of variations over space and time in the data (He and Huang, 2018; Huang et al., 2010).

To accurately attribute air pollution exposure to the study participants, we recorded the latitude and longitude of their mailing addresses as provided during their medical visits for the precise delivery of medical reports. These geographical coordinates were used to calculate the address-specific annual concentrations of $PM_{2.5}$. To evaluate chronic exposure to air pollution, we considered the 2-year average concentrations of $PM_{2.5}$, NO_2, and O_3, which encompass the year prior to and the year of the medical examinations.

2.4. Covariates

Covariates were selected a priori, mainly based on literature review (Deng et al., 2023 Kim et al., 2019). The questionnaire, completed by participants themselves, gathered data on demographic factors, lifestyle choices, and personal health histories. Height and weight measurements were taken using a Nakamura anthropometer (model KN-5000A, Tokyo, Japan) with participants dressed in light indoor attire and barefoot. The Body Mass Index (BMI, kg/m^2) was determined by dividing the body weight in kilograms by the square of the height in meters.

2.5. Statistical analysis

All analyses were conducted utilizing R software version 4.0.3 (R Core Team, Vienna, Austria). Pearson correlation was employed to ascertain the interrelationships among various air pollutants. For assessing the associations between air pollution, NAFLD, and advanced fibrosis, a logistic regression approach was selected, and odds ratios (OR) with 95% confidence intervals (CI) were computed for each pollutant. Building on existing literature (Jung et al., 2019; Kim et al., 2020; Zhang et al., 2019), four progressively detailed models were defined: Model 1 included no adjustments; Model 2 accounted for age (in years) and sex (male or female); Model 3 incorporated additional variables including smoking status (never, former, or current), alcohol consumption ($<$1, 1–3, or 3–6 times/week), educational attainment ($<$10, 10–12, 13–16, or $>$16 years), BMI (kg/m^2, as a continuous measure), physical activity (categorized as low $<$3.75; moderate 3.75–10.31; or high $>$10.31 METs, where MET is defined as 1 kcal/kg/hour) (Lao et al., 2018)), fruit consumption ($<$1, 1–2, or $>$2 servings/day), vegetable consumption ($<$1, 1–2, or $>$2 servings/day), exposure to occupational dust/organic solvents (yes or no), and seasonality; model 4 further adjusted for hypertension (as defined by systolic BP $\geq$140 mm Hg and/or diastolic BP $\geq$90 mm Hg, or self-reported physician-diagnosed hypertension), diabetes (as defined by FPG $\geq$7 mmol/l, or self-reported physician-diagnosed diabetes), and dyslipidemia (as defined by total cholesterol $\geq$240 mg/dL, triglycerides $\geq$200 mg/dL, or HDL cholesterol $<$40 mg/dL).

Stratified analysis was conducted to investigate the potential modifying influences of age ($<$65 or $\geq$65 years), sex (male or female), alcohol intake ($<$3 or 3–6 times/week), smoking (never or ever), and physical activity levels (low or moderate to high) on the link between air pollution and NAFLD/advanced fibrosis. This was done by introducing an interaction term that multiplied each potential modifier with the continuous variable of air pollutant concentration.

To validate the robustness of the results, six sensitivity analyses were performed: 1) using a 1-year average of air pollution to assess long-term exposure; 2) re-evaluating the data excluding participants with a history of hypertension, cardiovascular disease, stroke, or cancer to minimize the potential influence of comorbidities; 3) applying two-pollutant models to assess the confounding effects of co-occurring pollutants; and 4) examining the link between air pollution and NAFLD/advanced fibrosis within the Taiwan population to determine if the outcomes were consistent across different groups; 5) further adjusting for region of participant's location (Taiwan and Hong Kong) to consider the effects of different regions; 6) introducing calendar year as an additional covariate to account for potential effect of time-related confounding factor.

3. Results

3.1. General characteristics

The general information of included participants is depicted in Table 1. We recruited 329,048 participants in the current data analysis. These participants averaged 41.0$\pm$13.0 years at baseline, and 43.7% were males. The majority of the included participants were never smokers, had a college education or higher, and drank alcohol less than 1 time per week. Compared with the overall participants, those with NAFLD or advanced fibrosis was older and more likely to be females, had higher BMI and WC, and higher prevalence of hypertension and diabetes.

Fig. 1 shows the distributions of exposure to each air pollutant. The mean (SD) two-year levels of $PM_{2.5}$, NO_2 and O_3 were 26.3 (7.5), 43.4 (18.9) and 52.0 (9.9) μg/m^3, respectively. The correlations between the pollutants were heterogeneous (Figure S2), with weak positive

Table 1
General characteristics of the participants.

Characteristics	All participants	Participants with NAFLD	Participants with advanced fibrosis
Total number	329,048	96,852	67,930
Age (year)	41.0(13.0)	43.6(13.8)	45(14.7)
BMI (kg/m^2)	23.0(3.7)	26.3(4.1)	25.2(3.8)
WC (cm)	76.3(10.4)	83.7(11.8)	79.7(11)
Male (n, %)	143,884 (43.73%)	40740(42.06%)	16491(24.28%)
Hypertension (n, %)	47937 (14.57%)	24499(25.3%)	15981(23.53%)
Diabetes (n, %)	12996 (3.95%)	8597(8.88%)	6898(10.15%)
Education (n, %)			
Lower than high school	48559 (14.76%)	22678(23.42%)	19223(28.3%)
High school	65090 (19.78%)	20209(20.87%)	14124(20.79%)
College or university	173461 (52.72%)	44825(46.28%)	29396(43.27%)
Postgraduate	41938 (12.75%)	9140(9.44%)	5187(7.64%)
Smoking (n, %)			
Never	253789 (77.13%)	72869(75.24%)	56835(83.67%)
Former	18027 (5.48%)	5717(5.9%)	3069(4.52%)
Current	57232 (17.39%)	18266(18.86%)	8026(11.82%)
Alcohol use (n, %)			
< 1 time/week	287383 (87.34%)	82419(85.1%)	59921(88.21%)
1–3 times/week	31658 (9.62%)	10394(10.73%)	5642(8.31%)
3–6 times/week	10007 (3.04%)	4039(4.17%)	2367(3.48%)
Physical activity			
Low	140497 (42.7%)	44015(45.45%)	30150(44.38%)
Moderate	26111 (7.94%)	5354(5.53%)	3395(5%)
High	162440 (49.37%)	47483(49.03%)	34385(50.62%)
Vegetable intake (n, %)			
Seldom	56137 (17.06%)	17578(18.15%)	12436(18.31%)
Moderate	184509 (56.07%)	53494(55.23%)	37194(54.75%)
Frequent	88402 (26.87%)	25780(26.62%)	18300(26.94%)
Fruit intake (n, %)			
Seldom	108254 (32.9%)	31779(32.81%)	21052(30.99%)
Moderate	181060 (55.03%)	53340(55.07%)	38270(56.34%)
Frequent	39734 (12.08%)	11733(12.11%)	8608(12.67%)
Occupational exposure (n, %)	23851 (7.25%)	6569(6.78%)	3790(5.58%)
AST (IU/L)	22.7(14.0)	25.7(19.4)	22.7(19.4)
ALT (IU/L)	25.9(25.8)	31.3(33.6)	18.8(19.8)
GGT (IU/L)	25.0(31.0)	35(48.6)	23.3(40.1)
$PM_{2.5}$ (μg/m^3)	26.3(7.5)	26.9(7.8)	26.9(7.8)
NO_2 (μg/m^3)	43.4(18.9)	43.8(19.1)	44(19.4)
O_3 (μg/m^3)	52.0(9.9)	51.7(10.4)	51.4(10.7)

Abbreviations: NAFLD: non-alcoholic fatty liver disease; BMI: body mass index; WC: waist circumference; AST: aspartate aminotransferase; ALT: alanine aminotransferase; GGT: γ-glutamyl transferase; PM2.5: particulate matter ≤ 2.5 μm; NO2: nitrogen dioxide; O3: ozone

coefficients between $PM_{2.5}$ and NO_2 (Pearson's r = 0.1) and weak negative coefficients between $PM_{2.5}$ and O_3 (Pearson's r = −0.1). Ambient O_3 had a strongly negative correlation with NO_2 (Pearson's r = −0.8).

3.2. Relationship between air pollution and NAFLD and advanced fibrosis

The relationships of ambient air pollution with the likelihood of having NAFLD and advanced fibrosis are depicted in Table 2 and Fig. 2. In our main analysis, we developed four models and incrementally adjusted for age, sex, BMI, smoking, alcohol drinking, educational level, physical activity, fruit intake, vegetable intake, occupational exposure to dust/organic solvents, season, hypertension, type 2 diabetes, and dyslipidaemia. We observed consistent associations across the four models for all three air pollutants. The results suggested that both $PM_{2.5}$ and NO_2 were positively associated with higher prevalence of NAFLD, with ORs of 1.10 (95% CI: 1.09–1.11) for every SD increase in $PM_{2.5}$ and 1.08 (95% CI: 1.07–1.09) for NO_2. Similarly, $PM_{2.5}$ and NO_2 were positively associated with advanced fibrosis, with ORs of 1.08 (95% CI: 1.07–1.09) for every SD increase in $PM_{2.5}$ and 1.07 (1.06–1.08) for NO_2. In contrast, ambient O_3 was negatively associated with both NAFLD and advanced fibrosis, every SD increase in O_3 exposure was associated with ORs of 0.88 (0.87–0.89) for NAFLD and 0.89 (0.88–0.91) for advanced fibrosis, respectively.

3.3. Stratified and sensitivity analysis

In subgroup analyses for NAFLD (Table S1), significantly stronger effect estimates were generally observed in females, younger adults (aged<65 y), and never smokers for all three air pollutants. Participants drank alcohol less than 3 time/week had larger effect estimates for O_3. Participants with low physical activity had stronger effect estimates for NO_2 and O_3 than those with moderate to high physical activity.

In subgroup analyses for advanced fibrosis (Table S2), we observed heightened effects in females for all three air pollutants. Younger adults (aged<65 y) and participants drank alcohol less than 3 time/week had stronger associations with $PM_{2.5}$ and O_3. Never smokers had a stronger association with $PM_{2.5}$ and NO_2 comparing to ever smokers. Participants with low physical activity had stronger associations with NO_2 and O_3 comparing to those with moderate to high physical activity.

The results of the sensitivity analyses for both NAFLD and advanced fibrosis (Table S3) yielded generally similar results.

3.4. Two-pollutant model effects

In the two-pollutant models (Table S4), the relationships between $PM_{2.5}$ and NAFLD and advanced fibrosis were robust after adjusting for NO_2 or O_3. And the effect estimates for NO_2 were not significantly changed by adjustment for $PM_{2.5}$. Similarly, the associations between O_3 and NAFLD and advanced fibrosis remained stable despite adjustment for $PM_{2.5}$ or NO_2. However, the associations between NO_2 and NAFLD and NAFLD-related advanced fibrosis became negative after O_3 adjustment.

4. Discussion

We conducted a large population-based study of more than 300,000 participants and observed higher prevalent NAFLD and advanced fibrosis with chronic $PM_{2.5}$ and NO_2 exposure. Ambient O_3 exposure was related with lower odds of NAFLD and advanced fibrosis.

To the best of our knowledge, we firstly examined the link between multiple air pollutants and NAFLD-related advanced fibrosis in high-income Asia population. Our findings of the positive association between ambient air pollution and prevalent NAFLD are in line with some previous studies. Long-term exposure to $PM_{2.5}$ has been reported to be associated with increases risk of NAFLD in China (Deng et al., 2023), Germany(Matthiessen et al., 2023), and UK (Li et al., 2023). In addition, the UK Study also found that every interquartile range increase in PM_{10}, NO_2 and NOx exposures was associated with 14% (95%CI: 9%-20%), 19% (13%-24%), and 11% (7%, 15%) increased risk of NAFLD, respectively (Li et al., 2023). What's more, our results are also consistent

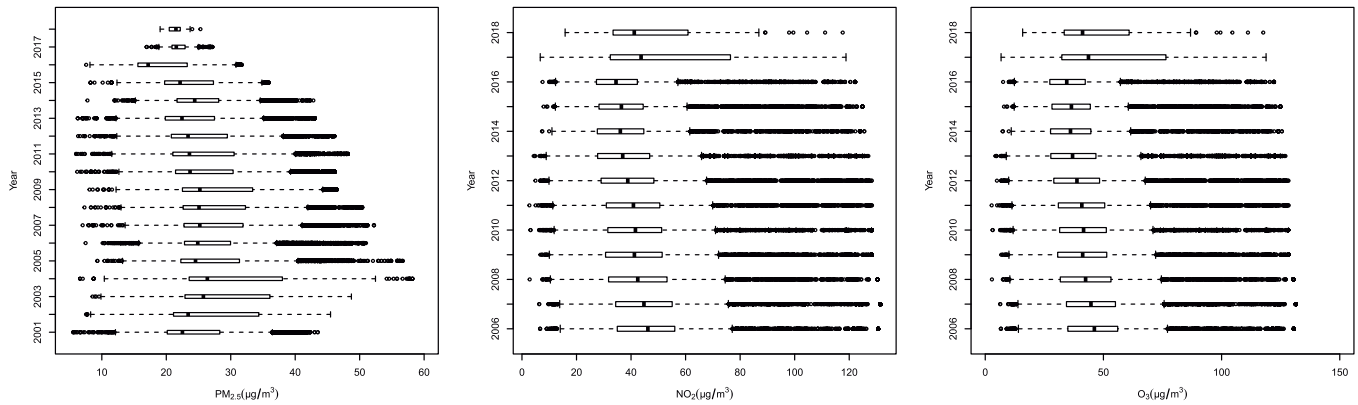

Fig. 1. The temporal distribution of the two-year average concentrations of $PM_{2.5}$, NO_2 and O_3 by year in Taiwan and Hong Kong. The boxes indicate the 25–75th percentiles (IQR) and the centre lines indicate the median concentrations. The whiskers extend to the highest observations within three IQRs of the box, with more extreme observations shown as circles.

Table 2
Associations between long-term air pollution exposure and NAFLD and NAFLD-related advanced fibrosis.

Air pollution exposure	Model 1		Model 2		Model 3		Model 4	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
NAFLD								
$PM_{2.5}$, μg/m^3								
1st Quartile (< 21.40)	Ref		Ref		Ref		Ref	
2nd Quartile (21.40–23.90)	1.04(1.02–1.06)	0.001	1.06 (1.04–1.08)	<0.001	1.08 (1.05–1.11)	<0.001	1.07 (1.04–1.11)	<0.001
3rd Quartile (23.90–29.39)	1.07(1.04–1.09)	<0.001	1.09 (1.07–1.11)	<0.001	1.08 (1.05–1.11)	<0.001	1.07(1.04–1.10)	<0.001
4th Quartile (29.39–58.18)	1.26(1.23–1.29)	<0.001	1.25 (1.22–1.28)	<0.001	1.27 (1.23–1.30)	<0.001	1.28 (1.24–1.31)	<0.001
P for trend		<0.001		<0.001		<0.001		<0.001
Per SD (7.5 μg/m^3) increment	1.11(1.10–1.11)	<0.001	1.10 (1.09–1.11)	<0.001	1.10 (1.01–1.11)	<0.001	1.10 (1.09–1.11)	<0.001
NO_2, μg/m^3								
1st Quartile (< 30.52)	Ref		Ref				Ref	
2nd Quartile (30.52–40.27)	1.06(1.03–1.09)	<0.001	1.07(1.04–1.10)	<0.001	1.12 (1.08–1.16)	<0.001	1.11 (1.06–1.15)	<0.001
3rd Quartile (40.27–50.51)	1.08(1.05–1.11)	<0.001	1.10(1.07–1.13)	<0.001	1.13 (1.09–1.18)	<0.001	1.13 (1.09–1.18)	<0.001
4th Quartile (50.51–131.40)	1.08(1.05–1.11)	<0.001	1.11(1.08–1.14)	<0.001	1.22 (1.17–1.26)	<0.001	1.21 (1.17–1.26)	<0.001
P for trend		<0.001		<0.001		<0.001		<0.001
Per SD(18.9 μg/m^3) increment	1.02 (1.01–1.03)	<0.001	1.03(1.02–1.04)	<0.001	1.08 (1.06–1.09)	<0.001	1.08 (1.07–1.09)	<0.001
O_3, μg/m^3								
1st Quartile (< 46.44)	Ref		Ref				Ref	
2nd Quartile (46.44–53.64)	0.93 (0.90–0.95)	<0.001	0.91 (0.88–0.94)	<0.001	0,79 (0.76–0.82)	<0.001	0.79 (0.76–0.82)	<0.001
3rd Quartile (53.64–58.68)	0.97 (0.95–1.00)	0.038	0.95 (0.93–0.98)	<0.001	0.84 (0.81–0.87)	<0.001	0.82 (0.79–0.85)	<0.001
4th Quartile (58.68–81.37)	0.95 (0.93–0.98)	<0.001	0.93 (0.90–0.95)	<0.001	0.79 (0.76–0.82)	<0.001	0.78 (0.75–0.81)	<0.001
P for trend		0.016		<0.001		<0.001		<0.001
Per SD(9.9 μg/m^3) increment	0.96 (0.95–0.97)	<0.001	0.95 (0.95–0.96)	<0.001	0.88 (0.87–0.90)	<0.001	0.88 (0.87–0.89)	<0.001
Fibrosis								
$PM_{2.5}$, μg/m^3								
1st Quartile (< 21.40)	Ref		Ref				Ref	
2nd Quartile (21.40–23.90)	1.01 (0.98–1.03)	0.596	1.04 (1.01–1.07)	0.002	1.05 (1.01–1.08)	<0.001	1.05 (1.02–1.08)	0.002
3rd Quartile (23.90–29.39)	1.00 (0.98–1.03)	0.886	1.04 (1.02–1.07)	0.002	1.02 (0.99–1.05)	<0.001	1.03 (1.00–1.06)	0.032
4th Quartile (29.39–58.18)	1.24 (1.21–1.27)	<0.001	1.23 (1.21–1.27)	<0.001	1.19 (1.16–1.23)	<0.001	1.21 (1.18–1.24)	<0.001
P for trend		<0.001		<0.001		<0.001		<0.001
Per SD (7.5 μg/m^3) increment	1.10 (1.09–1.11)	<0.001	1.09 (1.09–1.10)	<0.001	1.07 (1.06–1.08)	<0.001	1.08 (1.07–1.09)	<0.001
NO_2, μg/m^3								
1st Quartile (< 30.52)	Ref		Ref				Ref	
2nd Quartile (30.52–40.27)	1.02 (0.99–1.06)	0.144	1.04 (1.00–1.07)	0.038	1.06 (1.02–1.09)	<0.001	1.06 (1.02–1.10)	0.002
3rd Quartile (40.27–50.51)	1.08 (1.05–1.11)	<0.001	1.09 (1.06–1.13)	<0.001	1.11 (1.07–1.15)	<0.001	1.11 (1.07–1.16)	<0.001
4th Quartile (50.51–131.40)	1.08 (1.05–1.12)	<0.001	1.10 (1.07–1.14)	<0.001	1.16 (1.11–1.20)	<0.001	1.16 (1.12–1.20)	<0.001
P for trend		<0.001		<0.001		<0.001		<0.001
Per SD(18.9 μg/m^3) increment	1.03 (1.02–1.05)	<0.001	1.04 (1.03–1.06)	<0.001	1.07 (1.05–1.08)	<0.001	1.07 (1.06–1.08)	<0.001
O_3, μg/m^3								
1st Quartile (< 46.44)	Ref		Ref				Ref	
2nd Quartile (46.44–53.64)	0.91 (0.88–0.94)	<0.001	0.89 (0.86–0.92)	<0.001	0.84 (0.81–0.88)	<0.001	0.84 (0.81–0.87)	<0.001
3rd Quartile (53.64–58.68)	0.92 (0.89–0.95)	<0.001	0.91 (0.89–0.94)	<0.001	0.85 (0.82–0.88)	<0.001	0.85 (0.82–0.88)	<0.001
4th Quartile (58.68–81.37)	0.90 (0.87–0.93)	<0.001	0.89 (0.86–0.91)	<0.001	0.81 (0.78–0.84)	<0.001	0.81 (0.78–0.84)	<0.001
P for trend		<0.001		<0.001		<0.001		<0.001
Per SD(9.9 μg/m^3) increment	0.93 (0.92–0.94)	<0.001	0.93 (0.92–0.94)	<0.001	0.90 (0.88–0.91)	<0.001	0.89 (0.88–0.91)	<0.001

Abbreviations: PM2.5: particulate matter ≤ 2.5 μm; NO2: nitrogen dioxide; O3: ozone; SD: standard deviation; OR: odds ratio; CI: confidence interval
Model 1 was not adjusted. Model 2 was adjusted for age and sex. Model 3 was further adjusted for smoking, alcohol use, educational level, physical activity, fruit intake, vegetable intake, BMI, occupational exposure to dust/organic solvents, and season. Model 4 further adjusted for hypertension, type 2 diabetes, and dyslipidaemia

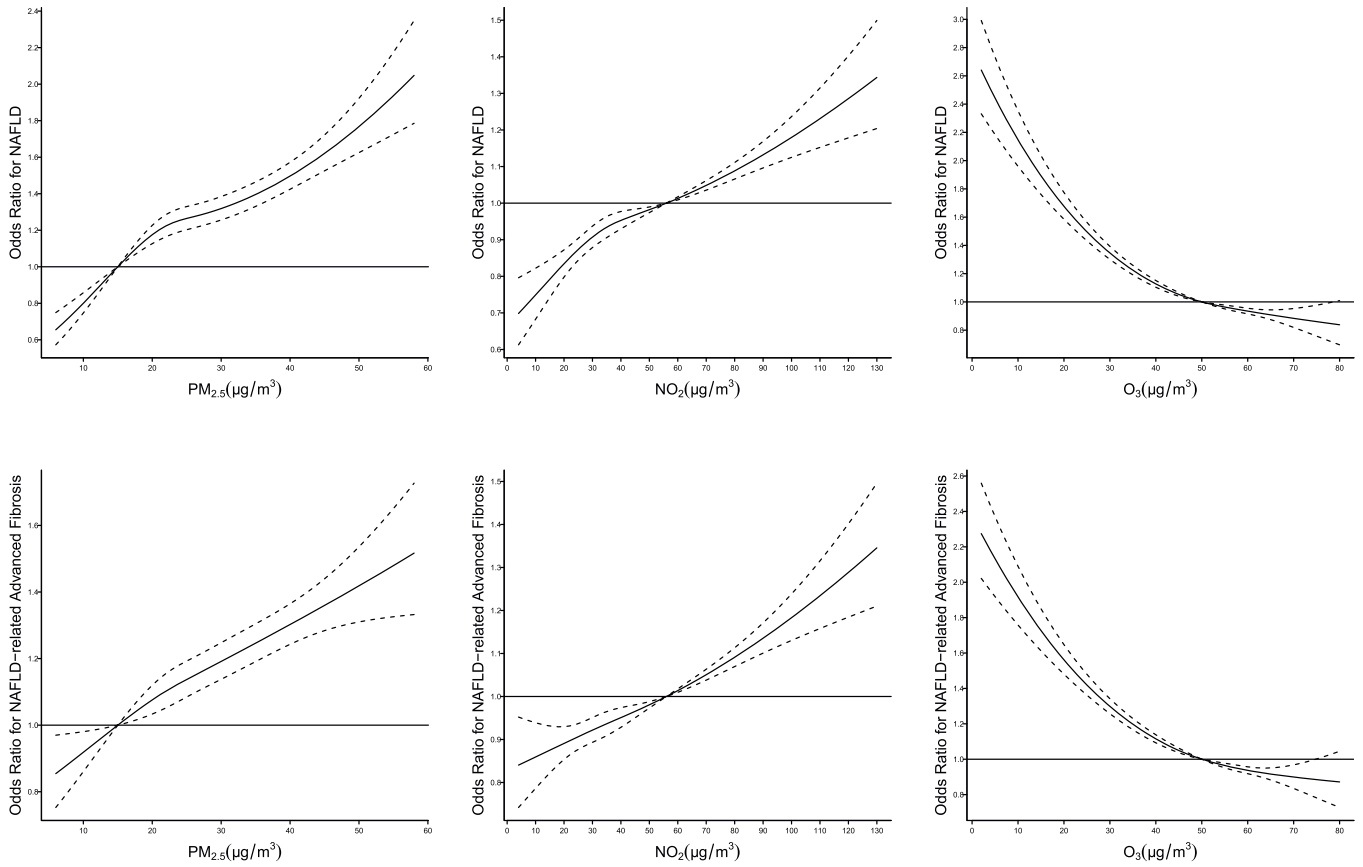

Fig. 2. Shapes of the concentration–response relationships of $PM_{2.5}$, NO_2 and O_3 and the prevalence of NAFLD and advanced fibrosis.

with a number of previous studies which investigated the relationships of ambient air pollutants with MAFLD (Guo et al., 2022) or liver enzymes (Hsieh et al., 2018; Kim et al., 2019; Markevych et al., 2013; Zhang et al., 2019). A cross-sectional study among 90,086 Chinese adults revealed that PM_1, $PM_{2.5}$, PM_{10}, and NO_2 were all associated with higher odds of MAFLD (Guo et al., 2022). Another cross-sectional study among 36,151 Korean adults revealed that chronic exposure to air pollution (i.e., PM_{10}, NO_2, SO_2, CO) was positively associated with higher ALT and AST (Kim et al., 2019). Our previous study based on the Taiwan cohort also found that every 10 $\mu g/m^3$ increasement in the 2-year mean $PM_{2.5}$ was associated with increased ALT and GGT levels (Zhang et al., 2019). However, the results of two studies from the U.S. were inconsistent with our findings. Markevych and colleagues evaluated the relationships of ambient $PM_{2.5}$, PM_{10}, PM_{coarse}, NO_X and NO_2 with AST, ALT and GGT. They found a significantly positive association only between $PM_{2.5}$ and GGT; no significant relationships were observed between other air pollutants and liver enzymes (Markevych et al., 2013). A study among 74 U.S. children reported that traffic-related air pollution had non-significant relationships with AST and ALT but a significant association with cytokeratin-18, a marker of hepatocellular apoptosis (Hsieh et al., 2018). These inconsistencies may be attributable to various factors, including differences in the study populations, study designs, study regions, and the concentration and composition of air pollutants. In addition, it is difficult to compare these results with our study because the different health outcomes, and the concentration and composition of air pollutants.

We observed inverse relationships between O_3 and the prevalence of NAFLD and advanced fibrosis, which is in contrast to the findings of a Korean study reporting a positive association between short-term exposure to O_3 and GGT (Kim et al., 2015). A possible reason is the strongly negative correlation with NO_2 observed in our study (Pearson's $r = -0.80$). In the Korean study, the correlation between O_3 and NO_2 was weak (Pearson's $r = -0.1512$). In addition, the concentrations of O_3 in our study regions (mean [SD]: 52.0 ± 9.9 $\mu g/m^3$) were lower and less variable than those observed in the previous Korean study [mean (SD): 47.6 ± 27.4 ppb (approximately 95.2 $\mu g/m^3$)]. Previous study suggested that low-dose ozone can exert biological regulatory effects by restoring redox signaling and improving antioxidant capacity (Viebahn-Haensler and León Fernández, 2021). In addition, Díaz et al. found a U-shaped relationship between O_3 and daily mortality (Díaz et al., 2018). Therefore, the relatively low concentrations of O_3 in Hong Kong and Taiwan may contribute to the beneficial effects of O_3 on odds of NAFLD. What's more, our results parallel those from another Chinese study. Qiu and colleagues (Qiu et al., 2021) conducted a panel study among 3892 adults in urban China that had a slightly higher level of O_3 (mean (SD): 66.28 ± 20.8) than our study did. Further studies on the health effects of wider range of O_3 concentration on NAFLD are warranted.

In stratified analysis, we observed that the impacts of ambient air pollution on NAFLD and NAFLD-related advanced fibrosis were higher in the younger adults (aged<65 y). This difference may be partly explained by the reduced responsiveness to autonomic nervous system stimulation in older adults (Cohen et al., 2012). We also observed stronger associations between ambient air pollution exposure and NAFLD or NAFLD-related advanced fibrosis in females and never-smokers. It may be ascribed that females and males have different physiological and behavioral factors (such as temporal activity patterns), which can result in differential susceptibility (Wang et al., 2022). What's more, previous studies suggested that air pollution may interfere with estrogen-mediated regulation (Chen et al., 2013), smoking is more common among men and thus would affect the associations of air pollution with NAFLD.

In the two-pollutant models, $PM_{2.5}$ associations were robust to adjustment for NO_2 and O_3, and the estimated effects for NO_2 and O_3 were also not affected for $PM_{2.5}$ adjustment. We also found a weak

correlation between $PM_{2.5}$ and NO_2 concentrations in our study, which is consistent with previous studies from Taiwan (Wu et al., 2020) and Hong Kong (Chen et al., 2023). The weak correlation can be ascribed to different sources of $PM_{2.5}$ and NO_2. Normally, NO_2 is mostly derived from traffic emissions, power plants, and machinery. However, $PM_{2.5}$ is composed of different pollutant sources such as wind-blown dust, although usually it consists predominantly of chemical manufacturing industry, power industry, and manufacturing of coal-based product. Thus, the "alternative" sources, such as wind-blown dust, probably cause the weak correlation. In contrast to the generally robust $PM_{2.5}$ associations after adjustment for NO_2 and O_3, and NO_2/O_3 associations after adjustment for $PM_{2.5}$, we observed that single-pollutant OR estimates for NO_2 were positive for both outcomes but shifted to negative after adjustment for O_3. This might be due to the strong negative correlations between NO_2 and O_3 (Pearson's $r = -0.8$) in our study.

Potential mechanisms linking air pollution with NAFLD/advanced fibrosis are unclear. Animal model in mice suggested that exposure to high concentrations of $PM_{2.5}$ induces a non-alcoholic steatohepatitis-like phenotype and concomitant liver fibrosis by way of activating inflammatory response pathways mediated through nuclear factor kappa B (NF-κB), c-Jun N-terminal kinase (JNK), and Toll-like receptor 4 (TLR4) (Zheng et al., 2013). In rats, intragastric diesel exhaust particles resulted in oxidative stress, leading to DNA damage, as along with upregulating apoptosis and hepatic DNA repair.(Danielsen et al., 2008 Dybdahl et al., 2003) In addition, our previous studies suggested that long-term ambient air pollution exposure increase serum levels of liver damage biomarkers such as AST, ALT and GGT (Zhang et al., 2019).

This study has several important strengths. First, this study extended previous studies on the relationship between air pollution and fatty liver disease by including two populations from regions with a wide range of air pollution concentrations. Therefore, our findings are more generalizable than those examined only one specific area. Second, the large sample size in the current study enabled us to calculate precise and stable effect estimates. Third, we adopted a spatiotemporal model based on the satellite data to estimate each individual's air pollution exposure instead of using data from monitoring stations, which diminished the problems of spatial coverage and interpolation.

The study has several limitations as well. First, NAFLD (especially at the early stages) is an outcome that can be reversed. Thus, it is difficult to identify the endpoint and decide the temporal relationships in our study. Second, the concentrations of air pollutants were evaluated at fixed addresses, and the patterns of participants' activities were not taken into account. More advanced technology is needed to improve exposure assessment. Third, the participants included in this study were members of a paid association, and the majority of them were relatively well educated and economically affluent. Therefore, caution should be exercised when generalising the results to other populations. Fourth, we used two non-invasive panels rather than ultrasound scans to diagnose NAFLD, which may lead to misclassification. However, it is not practical to use ultrasound scans in large-scale epidemiological studies because of the costs and logistic arrangements involved. However, the use of two non-invasive panels minimised the likelihood of misclassification. In addition, these panels have been externally validated and widely used in previous epidemiological studies (Bedogni et al., 2006 Hajifathalian et al., 2019; Kim et al., 2020; Lee et al., 2010; Meffert et al., 2014). Fifth, we excluded 102,373 participants (20.5%) with missing information on $PM_{2.5}$ or covariates, and the characteristics of included and excluded participants were slightly different. The participants included in this study were more educated, had slightly healthier behaviors, and had higher level of γ-glutamyl transferase than those excluded due to missing information on $PM_{2.5}$ or covariates. These issues may lead to potential selection bias and even bias the estimated associations. Therefore, it should be cautious to generalize these findings to other populations, and further studies with less selection of participants are warranted. However, the NAFLD prevalence in this study was similar to previously reported prevalence in Taiwan and other areas of China (29.4% vs. 26.17%–28.15%) (Global Burden of Disease Study, 2019). We also performed a series of subgroup analyses and sensitivity analyses, which took into account these variables. These findings yielded similar results, and the selection thus may not bring large bias in our main findings. Finally, only three pollutants were considered, the effects of other pollutants, such as PM_{10}, sulfur dioxide, and carbon monoxide, need to be assessed in future studies.

In conclusion, we found that in this large high income Asian population, long-term exposure to $PM_{2.5}$ and NO_2 is associated with higher prevalence of NAFLD and NAFLD-related advanced fibrosis. The associations with $PM_{2.5}$ exposure are stronger and more stable. Further investigation on the associations between O_3 exposure and NAFLD and NAFLD-related advanced fibrosis are warranted. Our findings indicate that exposure to $PM_{2.5}$ and NO_2 may be an important risk factor that can be modified by interventions for preventing NAFLD, a disease with no pharmacological treatment approved.

Author contribution

XQL conceived of and designed the study. CQL, BH, AKHL, and XQL acquired the data. YCB, and CG searched literature. YCB analysed the data, interpreted the results, and drafted the manuscript. All authors critically revised the manuscript. XQL obtained the funding. YH, MW, AKHL, and XQL supervised this study.

Fundings

This work described in this study was supported by Health and Medical Research Fund (18190131) and Research Grants Council of the Hong Kong Special Administrative Region (14109521). Dr. Cui Guo is supported by the RGC Postdoctoral Fellowship Scheme of the University Grants Committee of Hong Kong.

CRediT authorship contribution statement

Martin Wong: Writing – review & editing. **Bo Huang:** Writing – review & editing. **Alexis Lau:** Writing – review & editing, Methodology. **Yacong Bo:** Writing – original draft, Formal analysis, Data curation. **Changqing Lin:** Writing – review & editing, Methodology. **Cui Guo:** Writing – review & editing, Methodology. **Yu Huang:** Writing – review & editing. **Xiang Qian Lao:** Conceptualization.

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.

Data availability

Data will be made available on request.

Acknowledgement

Part of the data was provided by MJ Health Research Foundation (Authorization code: MJHR2019006A and MJHRF2021002A). Any interpretation or conclusion described in this paper does not represent the views of MJ Health Research Foundation.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ecoenv.2024.116245.

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