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Original article

Long-term exposure to ambient air pollution and serum liver enzymes in older adults: A population-based longitudinal study

Yingxin Li, MD[a,1], Xueli Yuan, MD[b,1], Jing Wei, PhD[c], Yuanying Sun, MD[b], Wenqing Ni, MD[b], Hongmin Zhang, MD[b], Yan Zhang, MD[b], Rui Wang, MD[d], Ruijun Xu, MD[a], Tingting Liu, MD[a], Chunyu Yang, MD[a], Gongbo Chen, PhD[e], Jian Xu, MD, PhD[b,**], Yuewei Liu, MD, PhD[a,*]

[a] Department of Epidemiology, School of Public Health, Sun Yat-sen University, Guangzhou, Guangdong, China
[b] Department of Elderly Health Management, Shenzhen Center for Chronic Disease Control, Shenzhen, Guangdong, China
[c] Department of Atmospheric and Oceanic Science, Earth System Science Interdisciplinary Center, University of Maryland, College Park, MD, USA
[d] Luohu Center for Chronic Disease Control, Shenzhen, Guangdong, China
[e] Department of Occupational and Environmental Health, School of Public Health, Sun Yat-sen University, Guangzhou, Guangdong, China

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ABSTRACT

Purpose: To investigate the association of long-term exposure to ambient air pollution with serum liver enzymes in older adults.

Methods: In this longitudinal study, we investigated 318,911 adults aged 65 years or older and assessed their long-term residential exposure to particulate matter with an aerodynamic diameter ≤2.5 μm ($PM_{2.5}$), particulate matter with an aerodynamic diameter ≤10 μm (PM_{10}), sulfur dioxide (SO_2), nitrogen dioxide (NO_2), carbon monoxide (CO), and ozone (O_3). Linear mixed models and generalized linear mixed models were implemented for exposure-response analyses.

Results: Each interquartile range (IQR) increase of $PM_{2.5}$, PM_{10}, SO_2, NO_2, CO, and O_3 exposures was significantly associated with a 4.6%, 4.6%, 5.6%, 4.6%, 6.2%, and 3.6% increase in alanine aminotransferase (ALT), and a 4.6%, 5.2%, 3.6%, 3.3%, 6.1%, and 4.0% increase in aspartate aminotransferase (AST), respectively. Each IQR increase of $PM_{2.5}$, PM_{10}, SO_2, NO_2, CO, and O_3 exposures was significantly associated with a 23%, 24%, 28%, 17%, 31%, and 19% increase in odds of elevated ALT (>40 U/L), and a 32%, 39%, 40%, 32%, 57%, and 25% increase in odds of elevated AST (>40 U/L), respectively.

Conclusions: Long-term exposure to ambient air pollution was significantly associated with increased serum liver enzyme levels in older adults, suggesting that air pollution exposures may induce hepatocellular injury.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CHAP, ChinaHighAirPollutants; CI, confidence interval; CO, carbon monoxide; FBG, fasting blood glucose; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; NO_2, nitrogen dioxide; $PM_{2.5}$, particulate matter with an aerodynamic diameter ≤2.5 μm; PM_{10}, particulate matter with an aerodynamic diameter ≤10 μm; SD, standardized deviation; SO_2, sulfur dioxide; TC, total cholesterol; TG, triglyceride; O_3, ozone; OR, odds ratio; WC, waist circumference.

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.

* Corresponding author. Department of Epidemiology, School of Public Health, Sun Yat-sen University, 74 Zhongshan Second Road, Guangzhou, Guangdong 510080, China.
** Corresponding author. Department of Elderly Health Management, Shenzhen Center for Chronic Disease Control, 2021 Buxin Road, Shenzhen, Guangdong 518020, China.
E-mail addresses: anniexu73@126.com (J. Xu), liuyuewei@mail.sysu.edu.cn (Y. Liu).

[1] Yingxin Li and Xueli Yuan contributed equally to this work.

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Introduction

As a leading contributor to global disease burden, exposure to ambient air pollution increases morbidity and mortality from various diseases and continues to be a major health concern worldwide [1]. Extensive studies have linked ambient air pollution to the development of a wide range of chronic diseases, including cardiovascular diseases, respiratory diseases, malignant neoplasms, and digestive diseases [2–4], and have suggested that oxidative stress and inflammation are critical intermediates in the transduction of systemic toxicity associated with air pollutant exposures [5,6]. The liver can be a vulnerable target organ because accumulating evidence reveals that exposure to air pollution induces hepatic oxidative stress and accelerates liver inflammation and steatosis, which can result in the development and progression of chronic liver diseases [7–9]. As recent epidemiologic studies have reported significant associations of exposure to ambient air pollution with various liver diseases, including metabolic associated fatty liver disease, liver cirrhosis, and liver cancer [10–12], the potential adverse effects of ambient air pollution on the liver have drawn much concern globally.

Liver enzymes especially alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are two sensitive indicators of hepatocellular injury and have been widely used in liver disease detection by serum aminotransferase assays in clinical practices [13–15]. AST is present in the liver and other organs including cardiac muscle, skeletal muscle, kidney, and brain, while ALT is a more specific marker of hepatocellular injury, which is mainly present in the liver. As both ALT and AST are normally present in serum at low levels, the elevation of their levels can reflect potential hepatocellular injury [13]. In 2020, two *in vivo* studies found that exposure to air pollution significantly increased serum ALT and AST levels in mice, suggesting that exposure to air pollution may lead to liver damage [16,17]. However, to date only a handful of epidemiologic studies have explored the effects of ambient air pollution on liver enzyme levels, and the findings remain largely inconsistent [11,18–20]. In addition, previous studies mainly focused on the association between particulate pollution and liver enzyme levels, whereas much less is known about gaseous pollutant exposures.

Here, we conducted a large longitudinal study among over 0.31 million older adults in Shenzhen, China to assess the association of long-term exposure to ambient particulate matter with an aerodynamic diameter $\leq$2.5 μm ($PM_{2.5}$), particulate matter with an aerodynamic diameter $\leq$10 μm (PM_{10}), sulfur dioxide (SO_2), nitrogen dioxide (NO_2), carbon monoxide (CO), and ozone (O_3) with serum ALT and AST levels, and quantitatively explore its susceptible populations.

Methods

Study design and population

We conducted this population-based longitudinal study using health data from the Elder Health Management Program in Shenzhen, China, which is one of the ongoing National Basic Public Health Service programs and has been administrated by the Shenzhen Center for Chronic Disease Control since 2017. Located in the southern province of Guangdong, Shenzhen covered an area of 1997.5 square kilometers and a population of 17.6 million in 2020.

According to the Elder Health Management Program, adults who were 65 years or older and had resided in Shenzhen for at least half a year were eligible for free health management services, including an annual physical examination provided by one of 695 community health service centers in Shenzhen. The physical examination included anthropometric measurements, blood and urine tests, imaging analyses, and a standard self-administered questionnaire survey. Between January 1, 2018 and December 31, 2020, 361,329 older adults underwent at least one physical examination. By excluding adults <65 years, residing outside Shenzhen, and/or with missing information on educational attainment, alcohol consumption, height, weight, waist circumference (WC), and/or liver enzyme measurements, we included 318,911 older adults as study subjects in the final analyses. The detailed process of study subject selection is shown in Supplementary Fig. 1. This study was approved by the Ethical Committee of Shenzhen Center for Chronic Disease Control with a waiver of informed consent.

Exposure assessment

Daily grid data (spatial resolution: 10 km × 10 km) on 24-hour average $PM_{2.5}$, PM_{10}, SO_2, NO_2, CO concentrations, and maximum 8-hour average O_3 concentrations during 2015–2020 in Shenzhen, China was obtained from the validated ChinaHighAirPollutants (CHAP) dataset (https://weijing-rs.github.io/product.html), which was generated using our proposed machine-learning prediction model to provide high-resolution and high-quality ground-level air pollutants in China [21]. The overall cross-validated coefficient of determination (R^2) for $PM_{2.5}$, PM_{10}, SO_2, NO_2, CO, and O_3 was 0.91, 0.88, 0.84, 0.84, 0.80, and 0.87, respectively [1–3]. For each subject, we extracted daily concentration of each pollutant at the geocoded residential address from the CHAP dataset and calculated the annual average concentration during up to 3 years before the date of physical examination. The long-term exposure in our main analyses was defined as the mean of the 3 annual average concentrations before the date of physical examination.

Outcomes

The outcomes of interest included the level of serum ALT and AST and their elevation. The elevation of serum ALT and AST levels was both defined as >40 U/L [22,23]. A venous blood sample after 8 hours of fasting was collected to determine serum concentrations (U/L) of ALT and AST. The blood sample of each subject was analyzed immediately using an automatic biochemical analyzer in the qualified laboratory of the hospital which administrated the community health service center. To ensure the accuracy and stability of the measurements, internal and external quality control programs were routinely performed.

Covariates

Information on demographic characteristics, lifestyle factors, medical histories, and medication was self-reported by subjects who were assisted by trained medical staff during the physical examination. Educational attainment was classified as illiteracy, primary school, middle school or equivalent, high school or equivalent, and college or higher. For cigarette smoking, subjects were categorized into non–smokers (never smoked in the past life), former smokers (habitually smoked in the past but quitted for at least 1 month), and current smokers (habitually smoked currently). For alcohol consumption, subjects were divided into non–drinkers (almost never), non–habitual drinkers (6 times per week to once per month), and habitual drinkers (once per day or more). Physical activity was evaluated by the frequency of moderate- to vigorous-intensity physical activities (at least some sweating and shortness of breath caused by engaging in physical activity) per week, which was divided into never, less than once a week, once or more a week, and every day.

Height, weight, and WC were measured with subjects wearing light clothing and no shoes. Body mass index (BMI) was calculated

as the weight in kilograms divided by the square of the height in meters (kg/m^2) and categorized into underweight (<18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2), and obese (≥30 kg/m^2) [24]. Abdominal obesity was defined as WC ≥80 cm for women and ≥90 cm for men [25].

A calibrated sphygmomanometer was used to measure the seated bilateral blood pressure twice. We determined the blood pressure for each arm by averaging values of 2 repeated measurements and used the measurement of the arm with higher blood pressure values for analysis. Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg [26], self-reported physician-diagnosed hypertension, or those having a history of hospital admissions for hypertension or using anti–hypertensive medications. An 8-hour fasting venous blood sample was collected to determine fasting blood glucose (FBG), total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C). Diabetes was defined as FBG ≥7.0 mmol/L [27], self-reported physician-diagnosed diabetes, or those having a history of hospital admissions for diabetes or using anti–diabetic medications. Dyslipidemia was defined as TC ≥6.20 mmol/L, TG >2.25 mmol/L, HDL-C <1.03 mmol/L, LDL-C >4.13 mmol/L [28], or those using medications to treat dyslipidemia.

Statistical analysis

The correlation between air pollutant exposures was estimated by Spearman's correlation coefficients. We employed linear mixed models with a subject-specific random intercept to assess the association of long-term exposure to ambient air pollutants with serum ALT and AST levels, which were log-transformed due to their approximate log-normal distributions. Percent change (calculated as [exp (β) − 1] × 100) in ALT or AST level and its 95% confidence interval (CI) were estimated with each interquartile range (IQR) increase of pollutant exposure. In categorical analyses, we divided the pollutant exposure into 4 groups according to its quartiles and estimated the percent change using the first quartile as the reference level. The linear trend of estimated percent change across quartiles of exposure was examined by including the median of each quartile range as a continuous variable in the model. To investigate the association of exposure to air pollutants with the risk of liver enzyme elevation, we used generalized linear mixed models to estimate the odds ratio (OR) and the 95% CI of the elevation of ALT or AST level. All models were adjusted for sex, age, race, educational attainment, cigarette smoking, alcohol consumption, physical activity, BMI categories, abdominal obesity, hypertension, diabetes, dyslipidemia, year, and season at the date of physical examination to account for potential confounding effects.

We conducted stratified analyses by sex (female, male), age (<75, ≥75 years), BMI (normal weight, overweight + obese), cigarette smoking (non–smoker, ever smoker [former smoker + current smoker]), and alcohol consumption (non–drinker, ever drinker [non–habitual drinker + habitual drinker]), and used likelihood ratio tests to examine their potential effect modifications. To evaluate the robustness of our results, we performed several sensitivity analyses, including: 1) employing 2-pollutant models by further adjusting for each of the other air pollutant in the same model; 2) using a 1-year or 2-year average annual concentration before the date of physical examination as the exposure metric; 3) restricting analyses to subjects without hypertension, diabetes, or dyslipidemia; 4) restricting analyses to liver enzyme measurements at the first visit. All analyses were performed using R version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria). A 2-sided P <.05 was considered statistically significant.

Table 1
Characteristics of the study subjects in Shenzhen, China, 2018–2020

Characteristic	Value
No. of subjects	318,911
No. of observations	509,950
Sex, male	226,759 (44.5)
Age, years	
65–69	265,822 (52.1)
70–74	133,053 (26.1)
75–79	63,360 (12.4)
≥80	47,715 (9.4)
Race, Han	507,399 (99.5)
Educational attainment	
Illiteracy	36,913 (7.2)
Primary school	189,760 (37.2)
Middle school or equivalent	140,859 (27.6)
High school or equivalent	95,268 (18.7)
College or higher	47,150 (9.2)
Cigarette smoking	
Non–smoker	427,750 (83.9)
Former smoker	35,618 (7.0)
Current smoker	46,382 (9.1)
Alcohol consumption	
Non–drinker	433,557 (85.0)
Non–habitual drinker	52,422 (10.3)
Habitual drinker	23,971 (4.7)
Physical activity	
Never	84,014 (16.5)
Less than once a week	33,397 (6.6)
Once or more a week	53,679 (10.5)
Every day	338,784 (66.4)
BMI	
Underweight	18,007 (3.5)
Normal weight	316,108 (62.0)
Overweight	157,862 (31.0)
Obese	17,973 (3.5)
Abdominal obesity	299,349 (58.7)
Hypertension	318,508 (62.5)
Diabetes	148,632 (29.1)
Dyslipidemia	232,666 (45.6)
Year at physical examination	
2018	106,017 (20.8)
2019	161,864 (31.7)
2020	242,069 (47.5)
Season at physical examination	
Spring	163,181 (32.0)
Summer	185,856 (36.4)
Autumn	125,808 (24.7)
Winter	35,105 (6.9)

BMI, body mass index.
Value as n or n (%).

Results

Demographic characteristics of study subjects are presented in Table 1. During the study period, we included 318,911 subjects who underwent a total of 509,950 physical examinations. Among these subjects, 44.0% (n = 140,169) underwent 2 or 3 physical examinations. Mean age of the subjects was 71.4 years (standardized deviation [SD]: 5.5 years) and the age ranged from 65.0 to 120.4 years. The spatial distribution of subjects is illustrated in Supplementary Fig. 2.

Table 2 shows distributions of long-term exposure to each air pollutant and liver enzyme levels. The IQR of exposure to $PM_{2.5}$, PM_{10}, SO_2, NO_2, CO, and O_3 was 4.3 μg/m^3, 7.2 μg/m^3, 1.2 μg/m^3, 8.5 μg/m^3, 0.07 mg/m^3, and 4.9 μg/m^3, respectively. Elevated ALT and AST levels were identified for 5.9% (n = 29,909) and 4.1% (n = 21,120) of all observations, respectively. In the Spearman's correlation analyses, $PM_{2.5}$, PM_{10}, SO_2, NO_2, and CO exposures were strongly or moderately correlated (all r > .50 and P <.05) except for NO_2 and CO (r = 0.49, P <.05), while O_3 exposure was not correlated with exposure to other pollutants (all P <.05) (Supplementary Table 1).

Table 2
Distributions of long-term exposure to ambient air pollutants and level of liver enzymes in Shenzhen, China, 2018–2020

	Mean (SD)	Percentile				
		5th	25th	50th	75th	95th
$PM_{2.5}$, μg/m^3	28.1 (2.9)	24.1	25.8	27.7	30.1	33.3
PM_{10}, μg/m^3	46.4 (4.2)	40.4	43.0	46.0	50.2	52.9
SO_2, μg/m^3	7.9 (0.9)	6.7	7.2	7.8	8.4	9.8
NO_2, μg/m^3	33.6 (5.3)	25.0	29.3	33.9	37.9	41.8
CO, mg/m^3	0.73 (0.05)	0.66	0.69	0.72	0.76	0.81
O_3, μg/m^3	92.4 (3.9)	85.3	90.3	92.9	95.1	98.1
ALT, U/L	21.1 (21.2)	9.0	13.1	17.9	24.0	42.6
AST, U/L	23.6 (19.1)	14.0	18.0	21.6	26.0	38.4

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CO = carbon monoxide; NO_2 = nitrogen dioxide; O_3 = ozone; $PM_{2.5}$ = particulate matter with an aerodynamic diameter ≤2.5 μm; PM_{10} = particulate matter with an aerodynamic diameter ≤10 μm; SD = standardized deviation; SO_2 = sulfur dioxide.

Table 3
Estimated percent change (95% CI) of liver enzyme levels associated with long-term exposure to ambient air pollutants in Shenzhen, China, 2018–2020

Liver enzyme	Pollutant	Per IQR increase*	Quartile of exposure				
			Quartile 1 (Ref.)	Quartile 2	Quartile 3	Quartile 4	*P* for linear trend
ALT	$PM_{2.5}$	4.6 (4.3, 4.9)	0	−0.5 (−0.8, −0.1)	1.7 (1.3, 2.1)	5.6 (5.1, 6.1)	<.001
	PM_{10}	4.6 (4.2, 4.9)	0	−0.9 (−1.2, −0.5)	0.5 (0.1, 0.9)	5.4 (4.9, 5.9)	<.001
	SO_2	5.6 (5.3, 5.9)	0	3.9 (3.5, 4.3)	5.2 (4.7, 5.6)	9.8 (9.2, 10.5)	<.001
	NO_2	4.6 (4.4, 4.9)	0	3.5 (3.1, 3.9)	5.8 (5.4, 6.3)	9.3 (8.8, 9.7)	<.001
	CO	6.2 (5.8, 6.7)	0	0.6 (0.2, 1.0)	1.2 (0.7, 1.7)	7.7 (7.0, 8.4)	<.001
	O_3	3.6 (3.4, 3.9)	0	4.4 (4.0, 4.7)	3.3 (2.9, 3.8)	5.5 (5.0, 6.1)	<.001
AST	$PM_{2.5}$	4.6 (4.3, 4.8)	0	2.2 (1.9, 2.5)	5.6 (5.2, 5.9)	6.6 (6.2, 7.0)	<.001
	PM_{10}	5.2 (4.9, 5.4)	0	1.5 (1.2, 1.8)	4.4 (4.1, 4.7)	6.5 (6.1, 6.9)	<.001
	SO_2	3.6 (3.4, 3.9)	0	3.3 (3.0, 3.6)	5.1 (4.8, 5.5)	7.5 (7.0, 8.0)	<.001
	NO_2	3.3 (3.1, 3.5)	0	2.1 (1.8, 2.4)	4.5 (4.2, 4.8)	6.5 (6.1, 6.8)	<.001
	CO	6.1 (5.7, 6.5)	0	2.8 (2.5, 3.1)	5.3 (4.9, 5.7)	11.2 (10.6, 11.8)	<.001
	O_3	4.0 (3.8, 4.2)	0	5.6 (5.3, 6.0)	6.6 (6.3, 7.0)	8.1 (7.7, 8.6)	<.001

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CI = confidence interval; CO = carbon monoxide; IQR = interquartile range; NO_2 = nitrogen dioxide; O_3 = ozone; $PM_{2.5}$ = particulate matter with an aerodynamic diameter ≤2.5 μm; PM_{10} = particulate matter with an aerodynamic diameter ≤10 μm; SO_2 = sulfur dioxide.
* The IQR of exposure to $PM_{2.5}$, PM_{10}, SO_2, NO_2, CO, and O_3 was 4.3 μg/m^3, 7.2 μg/m^3, 1.2 μg/m^3, 8.5 μg/m^3, 0.07 mg/m^3, and 4.9 μg/m^3, respectively.

Table 4
Estimated odds ratio (95% CI) of elevated liver enzymes associated with long-term exposure to ambient air pollutants in Shenzhen, China, 2018–2020

Liver enzyme	Pollutant	Per IQR increase*	Quartile of exposure				
			Quartile 1 (Ref.)	Quartile 2	Quartile 3	Quartile 4	*P* for linear trend
ALT	$PM_{2.5}$	1.23 (1.20, 1.26)	1	0.96 (0.92, 1.00)	1.08 (1.04, 1.13)	1.28 (1.23, 1.34)	<.001
	PM_{10}	1.24 (1.21, 1.27)	1	1.03 (0.99, 1.07)	1.11 (1.07, 1.16)	1.34 (1.28, 1.39)	<.001
	SO_2	1.28 (1.24, 1.31)	1	1.12 (1.08, 1.17)	1.19 (1.14, 1.24)	1.42 (1.34, 1.50)	<.001
	NO_2	1.17 (1.14, 1.20)	1	1.03 (0.99, 1.07)	1.16 (1.11, 1.20)	1.34 (1.29, 1.39)	<.001
	CO	1.31 (1.26, 1.36)	1	1.05 (1.01, 1.09)	1.11 (1.06, 1.16)	1.41 (1.33, 1.50)	<.001
	O_3	1.19 (1.16, 1.22)	1	1.24 (1.19, 1.30)	1.25 (1.20, 1.31)	1.43 (1.36, 1.50)	<.001
AST	$PM_{2.5}$	1.32 (1.29, 1.36)	1	1.09 (1.04, 1.15)	1.29 (1.23, 1.35)	1.61 (1.53, 1.69)	<.001
	PM_{10}	1.39 (1.35, 1.43)	1	1.06 (1.01, 1.11)	1.28 (1.22, 1.34)	1.58 (1.50, 1.66)	<.001
	SO_2	1.40 (1.36, 1.44)	1	1.18 (1.12, 1.23)	1.31 (1.24, 1.37)	1.76 (1.65, 1.87)	<.001
	NO_2	1.32 (1.29, 1.36)	1	0.98 (0.94, 1.03)	1.17 (1.12, 1.22)	1.57 (1.50, 1.64)	<.001
	CO	1.57 (1.50, 1.64)	1	1.16 (1.11, 1.22)	1.44 (1.37, 1.53)	2.16 (2.01, 2.31)	<.001
	O_3	1.25 (1.22, 1.29)	1	1.36 (1.29, 1.43)	1.40 (1.32, 1.47)	1.59 (1.50, 1.68)	<.001

Abbreviations as in Table 3.
* The IQR of exposure to $PM_{2.5}$, PM_{10}, SO_2, NO_2, CO, and O_3 was 4.3 μg/m^3, 7.2 μg/m^3, 1.2 μg/m^3, 8.5 μg/m^3, 0.07 mg/m^3, and 4.9 μg/m^3, respectively.

Long-term exposure to $PM_{2.5}$, PM_{10}, SO_2, NO_2, CO, and O_3 was consistently associated with higher serum ALT and AST levels (Table 3). Each IQR increase of exposure to $PM_{2.5}$, PM_{10}, SO_2, NO_2, CO, and O_3 was significantly associated with a 4.6%, 4.6%, 5.6%, 4.6%, 6.2%, and 3.6% increase in ALT level, and a 4.6%, 5.2%, 3.6%, 3.3%, 6.1%, and 4.0% increase in AST level, respectively (all P <.05). In the categorical analyses, we observed that the percent change of both ALT and AST levels increased monotonically across quartiles of exposure to all air pollutants (all P for linear trend <.05).

As shown in Table 4, long-term exposure to $PM_{2.5}$, PM_{10}, SO_2, NO_2, CO, and O_3 was consistently associated with increased odds of serum ALT and AST elevation. Each IQR increase of exposure to $PM_{2.5}$, PM_{10}, SO_2, NO_2, CO, and O_3 was significantly associated with a 23%, 24%, 28%, 17%, 31%, and 19% increase in odds of elevated ALT, and a 32%, 39%, 40%, 32%, 57%, and 25% increase in odds of elevated AST, respectively (all P <.05). The categorical analyses yielded monotonically increasing trends of the ORs across quartiles of exposure to all air pollutants (all P for linear trend <.05).

In the stratified analyses, we observed significantly stronger associations of exposure to $PM_{2.5}$, PM_{10}, SO_2, CO, and O_3 with AST level, $PM_{2.5}$, SO_2, and CO with increased odds of elevated ALT level, and SO_2, NO_2, and CO with increased odds of elevated AST level in men, while stronger associations of exposure to O_3 with ALT level, and $PM_{2.5}$ and PM_{10} with increased odds of elevated AST were observed in women (all P for effect modification <.05). For age, stronger associations of exposure to $PM_{2.5}$, PM_{10}, and NO_2 with ALT and AST levels, CO and O_3 with ALT level, and NO_2 and O_3 with increased odds of elevated AST were identified in subjects aged <75 years, while stronger associations of exposure to O_3 with AST level, and SO_2 and CO with increased odds of elevated ALT

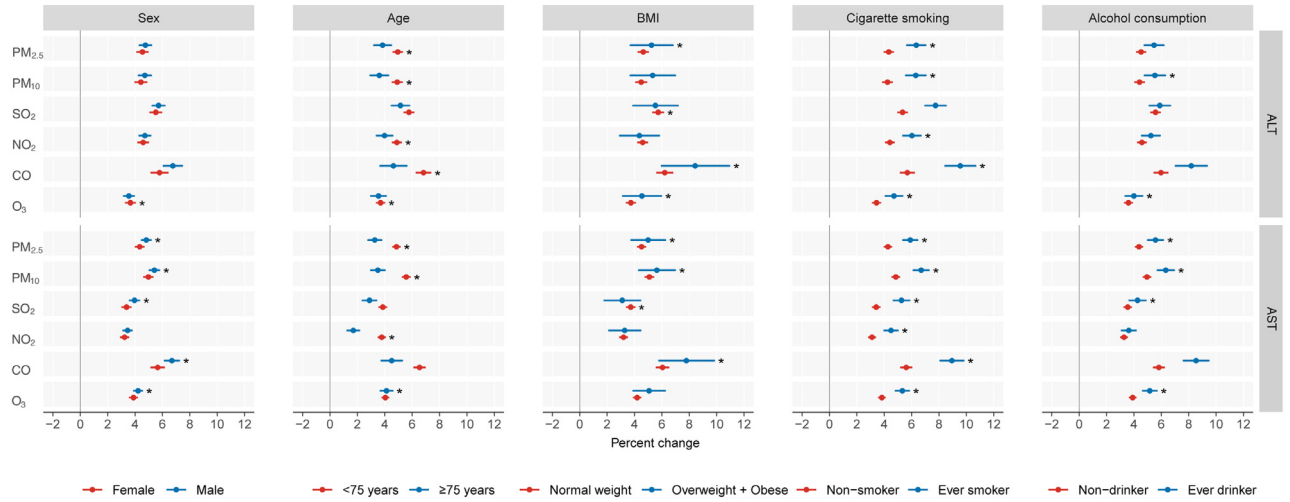

Fig. 1. Estimated percent change (95% CI) of liver enzyme levels associated with each IQR increase of exposure to ambient air pollutants in stratified analyses in Shenzhen, China, 2018–2020. ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMI = body mass index; CI = confidence interval; CO = carbon monoxide; IQR = interquartile range; NO_2 = nitrogen dioxide; O_3 = ozone; $PM_{2.5}$ = particulate matter with an aerodynamic diameter ≤2.5 μm; PM_{10} = particulate matter with an aerodynamic diameter≤10 μm; SO_2 = sulfur dioxide. The IQR of exposure to $PM_{2.5}$, PM_{10}, SO_2, NO_2, CO, and O_3 was 4.3 μg/m^3, 7.2 μg/m^3, 1.2 μg/m^3, 8.5 μg/m^3, 0.07 mg/m^3, and 4.9 μg/m^3, respectively. The asterisk indicates significant different associations by a given stratification variable.

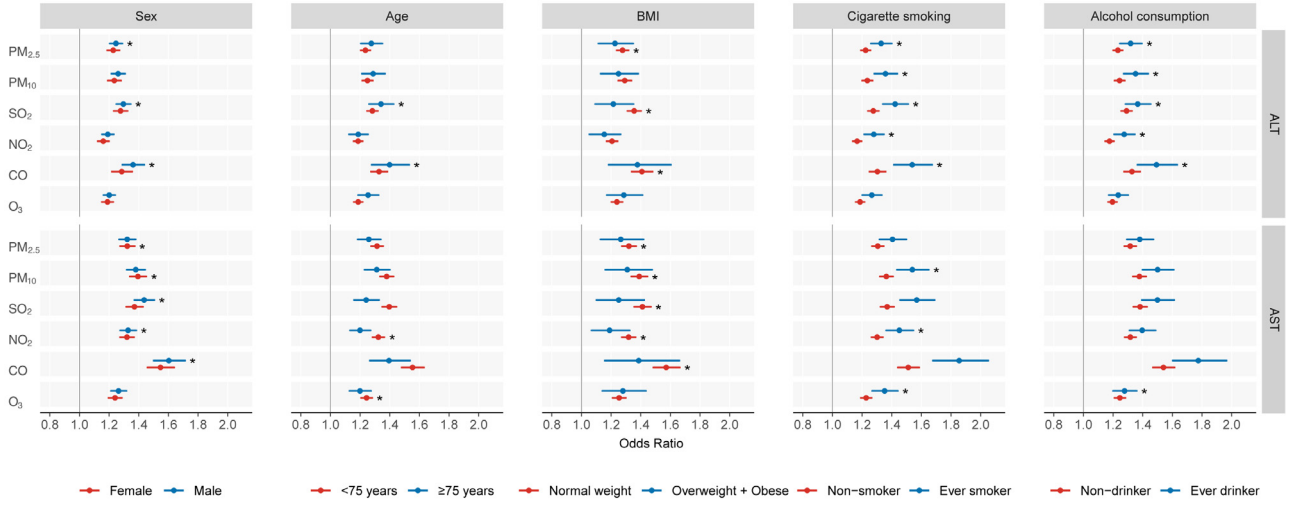

Fig. 2. Estimated odds ratio (95% CI) of elevated liver enzymes associated with each IQR increase of exposure to ambient air pollutants in stratified analyses in Shenzhen, China, 2018–2020. Abbreviations as in Fig. 1. The IQR of exposure to $PM_{2.5}$, PM_{10}, SO_2, NO_2, CO, and O_3 was 4.3 μg/m^3, 7.2 μg/m^3, 1.2 μg/m^3, 8.5 μg/m^3, 0.07 mg/m^3, and 4.9 μg/m^3, respectively. The asterisk indicates significant different associations by a given stratification variable.

were observed in subjects aged ≥75 years. For BMI, we observed stronger associations of exposure to $PM_{2.5}$, CO, and O_3 with ALT, $PM_{2.5}$, PM_{10}, and CO with AST in overweight or obese subjects and exposure to SO_2 with ALT and AST levels, $PM_{2.5}$, SO_2, and CO with increased odds of elevated ALT, and $PM_{2.5}$, PM_{10}, SO_2, NO_2, and CO with increased odds of elevated AST in subjects with normal weight. Stronger associations of exposure to $PM_{2.5}$, PM_{10}, NO_2, CO, and O_3 with both ALT and AST, SO_2 with AST, $PM_{2.5}$, PM_{10}, SO_2, NO_2, and CO with increased odds of elevated ALT, and PM_{10}, NO_2, and O_3 with increased odds of elevated AST were observed among ever smokers; likewise, we observed stronger associations among ever drinkers except for exposure to certain pollutants (Figs. 1 and 2). All sensitivity analyses yielded similar results (Supplementary Tables 2–9).

Discussion

In this large population-based longitudinal study of over 0.31 million older adults in Shenzhen, China, we quantitatively investigated the chronic effects of ambient air pollution on the level of liver enzymes. We found that long-term exposure to ambient $PM_{2.5}$, PM_{10}, SO_2, NO_2, CO, and O_3 was consistently associated with higher serum ALT and AST levels and increased odds of elevated serum ALT and AST levels. These associations were generally stronger among those who smoked or drank alcohol.

Previous studies on the association of long-term exposure to ambient air pollution with serum liver enzymes mainly focused on particulate pollution, especially $PM_{2.5}$. A study conducted in Taiwan in 2016 reported that each IQR (12.2 μg/m^3) increase of a 4-year average exposure to $PM_{2.5}$ was significantly associated with a 44.2% increase in ALT level, which was much higher than results from another study in Taiwan in 2019 and our study (0.74% and 13.6% per 12.2 μg/m^3 increase of $PM_{2.5}$ exposure) [11,20]. Consistent with our study, the Taiwan study in 2019 also identified significantly increased odds of elevated ALT and AST levels (OR: 1.09 and 1.06 per 10 μg/m^3 increase of $PM_{2.5}$ exposure), although the estimates were much lower than our results (OR: 1.62 and 1.91 per 10 μg/m^3 increase of $PM_{2.5}$ exposure) [20]. Note that the subjects

in the Taiwan study in 2019 were well-educated with an average age of 40.1 years, which may in part contribute to the high heterogeneity in comparison with the other Taiwan study and our study. In 2019, a cross-sectional study in Korea found that long-term exposure to PM_{10} was significantly associated with higher levels of ALT and AST [19], which was consistent with our results; however, a study in Germany did not identify any significant association of $PM_{2.5}$ or PM_{10} with ALT or AST [18], and the Taiwan study in 2019 reported insignificant association of $PM_{2.5}$ with AST [20].

To date, only a few studies have examined the association of long-term exposure to ambient gaseous pollutants, and the findings are mixed. Consistent with our results, the Korean study found that exposure to NO_2, SO_2, and CO was significantly associated with higher levels of ALT and AST [19]. A panel study in Korea also found that exposure to NO_2 was significantly associated with ALT and AST [29]. However, the German study did not identify any significant association of NO_2 with ALT or AST [18] and the panel study in Korea also did not identify any significant association of exposure to O_3 with ALT or AST [29]. The inconsistency among these studies may be due to differences in study population, study location, exposure level, and/or exposure assessment strategy.

The biological mechanisms linking air pollution and hepatocellular injury remain less clear. Several animal studies found that exposure to particulates led to oxidative stress in the liver, which could promote hepatic inflammatory infiltration and hepatocellular injury, and further induce chronic organic damage [8,30]. Inhaled particulates may activate resident phagocytic hepatic cells (e.g., Kupffer cells) and result in the activation of inflammatory response pathways in the liver [31], or indirectly affect the liver through the induction of proinflammatory milieu and dysregulated lipid homeostasis [32,33]. Although the biological evidence related to gaseous pollutants is limited, the hepatotoxicity induced by gaseous pollutants may share similar biomechanisms to particulates [34].

In this study, we found consistent stronger associations of exposure to all air pollutants with an increased level of liver enzymes among ever smokers, suggesting that smokers were more susceptible to ambient air pollutant exposures. Similar findings were also reported in the Taiwan study in 2019 [20]. Cigarette smoking is a well-documented factor to induce systematic oxidative stress [35], which may share similar pathways with air pollutant exposure to amplify its adverse effect on the liver. Consistent with results from the studies in Korea and Taiwan [19,20], we also found stronger associations among ever drinkers. Alcohol is known to cause hepatocellular injury and inflammation, which may interact with air pollution exposure and lead to abnormal liver enzyme levels [36]. Furthermore, our results show some evidence on the effect modification by sex, which was not observed for all studied pollutants. The possible biological explanations underlying the effect modification by sex included hormonally affected inflammation, airway reactivity, and anatomy and physiology of the respiratory system [37–39]. Further studies are warranted to better elucidate the susceptibility of different populations.

One unique strength of our study is the large sample size (over 0.31 million), which provides sufficient statistical power to generate robust results. Second, we investigated 6 ambient criteria air pollutants and employed 2-pollutant models to account for mutual effects of these air pollutants. Third, we estimated residential air pollutant exposures using a validated grid dataset, which had full coverage of the study area both spatially and temporally and enabled us to conduct individual-level exposure assessment with better accuracy than that based on city-level averages, land use regression, or spatial interpolation. Finally, we minimized confounding effects by taking into consideration a wide range of potential confounders including socioeconomic status, lifestyle factors, and clinical conditions.

Our study also has several limitations. First, since we conducted this study among adults aged 65 years or older, the generalization of our results is limited to older adults only. In addition, the pollutant exposure range was relatively narrow, which limited our ability to explore the associations under lower or higher exposures. Cautions should also be made to generalize the results to other regions or countries. Second, although this study is a longitudinal study, only 44.0% of the subjects underwent 2 or more physical examinations, which limited us to detect within-subject variations over time adequately. Third, since liver enzymes are present in some extrahepatic organs, elevations in liver enzymes can result from causes other than hepatocellular injury. Further studies using biomarkers with high hepatic specificity are needed to better characterize the effects of ambient air pollution on hepatocellular injury.

Conclusions

Long-term exposure to ambient air pollution was consistently associated with higher liver enzyme levels and increased odds of elevated liver enzyme levels in older adults, suggesting that exposure to ambient air pollution contributes to hepatocellular injury in older adults. These findings have significant implications for older adults, clinical practitioners, and public health policy makers that reducing individual exposure to ambient air pollution may help prevent hepatocellular injuries and liver diseases in older adults. Further studies are needed to confirm our results in other populations and elucidate underlying biological mechanisms.

Author contributions

Guarantor of the article: Yuewei Liu and Jian Xu. Study design: Yuewei Liu and Jian Xu. Data analysis: Yingxin Li, Xueli Yuan, Yuanying Sun, and Ruijun Xu. Data curation: Jian Xu, Yuewei Liu, Yuanying Sun, Wenqing Ni, Hongmin Zhang, and Yan Zhang. Air pollution data acquisition: Jing Wei and Yuewei Liu. Manuscript drafting: Yingxin Li and Xueli Yuan. Data interpretation and review and revision of the manuscript: All authors. Study concept and study supervision: Yuewei Liu and Jian Xu.

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Further reading

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