Association Between Ambient Volatile Organic Compounds and Hospital Admissions and Visits Due to Atopic Dermatitis and Asthma in Individuals Under the Age of 19 in Seoul

Minsun Lee

The Graduate School
Yonsei University
Department of Public Health

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This certifies that the Doctoral Dissertation

of Minsun Lee is approved.

Thesis Supervisor: Changsoo Kim

Myung Hyun Sohn: Thesis Committee Member #1

Jaelim Cho: Thesis Committee Member #2

Kyoung-Nam Kim: Thesis Committee Member #3

Dae Ryong Kang: Thesis Committee Member #4

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ABSTRACT

Association Between Ambient Volatile Organic Compounds and Hospital Admissions and Visits Due to Atopic Dermatitis and Asthma in Individuals Under the Age of 19 in Seoul

Minsun Lee

Department of Public Health
The Graduate School, Yonsei University
(Directed by Professor Changsoo Kim)

Background: Volatile organic compounds (VOCs) are a group of chemicals widely emitted from both anthropogenic and natural sources, contributing to air pollution and posing significant health risks. This study focuses on the short-term effects of ambient VOC mixtures on atopic dermatitis (AD) and asthma among individuals under the age of 19 in Seoul, South Korea. The research also aims to quantify the health and economic burdens associated with VOC exposure.

Methods: This study utilized data from 2015 to 2019, integrating daily hospital admission records for AD and asthma with ambient VOC concentration data from Seoul's monitoring stations. The analysis employed Generalized Additive Models (GAM), Weighted Quantile Sum Regression (WQSR), and Bayesian Kernel Machine Regression (BKMR) to assess both individual and combined effects of VOCs. Population Attributable Fractions (PAFs) and economic costs were estimated to evaluate the health burden of VOC exposure.

Results: The study identified significant associations between VOC exposure and increased hospital admissions for AD and asthma. Methylcyclopentane emerged as a key contributor to adverse health outcomes within the branched or cyclo-alkanes group. The combined effects of VOC mixtures were more pronounced compared to individual substances, highlighting the impact of chemical interactions. PAF analysis revealed that VOC exposure accounts for a measurable fraction of AD and asthma cases, with associated economic costs reflecting substantial healthcare burdens.

Conclusion: This research underscores the importance of addressing ambient VOC exposure, particularly among vulnerable populations such as children. Findings suggest that reducing emissions of key VOCs, including methylcyclopentane, could mitigate health risks and lower the burden of allergic diseases. The study provides a scientific foundation for targeted public health interventions and policy development to regulate harmful VOC emissions.

Key words : Volatile organic compounds, ambient exposure, atopic dermatitis, asthma, children

Ⅰ. INTRODUCTION

1. Background

Volatile organic compounds (VOCs) consist of thousands of chemicals found in various household products, industrial processes, and environmental settings [1]. VOCs also act as precursors in the form of ozone and secondary organic aerosols through photochemical reactions with nitrogen oxides (NOx) in the atmosphere [2]. They are emitted from a variety of sources, both anthropogenic and natural. Common sources include household products such as paints, cleaning agents, and personal care products; industrial emissions from manufacturing processes, petroleum refineries, and chemical plants; and outdoor sources such as vehicle exhaust, biomass burning, and natural emissions from vegetation [3, 4]. The diverse range of these sources contributes to the formation of an exposome comprising a variety of substances [5-8]. The average atmospheric lifespan of VOCs ranges from minutes to months [9].

The health hazards of VOCs, such as benzene, toluene, ethylbenzene, and xylenes at specific concentrations, have been extensively studied in several animal experiments [10-13]. The health effects of VOC exposure on various organ systems have been reported in occupational population studies [14-18] and indoor exposure studies [19-24]. A few epidemiological studies have explored the relationship between ambient VOC exposure and allergic, respiratory, cardiovascular, and hematologic diseases [9, 25-34]. These studies often focused on the effects of individual substances, but their findings were inconsistent with realistic scenarios involving interactions among multiple substances. In some cases, researchers

employed time-stratified conditional logistic regression and generalized estimating equations (GEE) to explore the link between VOCs and conditions such as urticaria and asthma, respectively [9, 27]. While they observed that VOC exposure was associated with an increased short-term risk of clinical visits and asthma symptoms, these approaches did not account for the combined effects of mutiple substances. With advancements in analytical modeling, methods such as Weighted Quantile Sum Regression (WQS) and Bayesian Kernel Maching Regression (BKMR), which are well-suited for mixed exposure analysis, have become more widely utilized [35-41].

Seoul, the capital of South Korea, has the largest population in the country and one of the highest rates of environmentally related diseases such as atopic dermatitis (AD) and asthma among children and adolescents [42]. In this study, we evaluated the short-term effects of ambient VOC compounds, both as individual substances and as mixtures, on hospital stays and visits for AD and asthma. Further, we estimated the disease burden in terms of population attributable fraction (PAF) and economic costs. Our findings have significant public health implications, highlighting the detrimental effects of VOC exposure on human health and emphasizing that reducing VOC exposure is an effective strategy for alleviating the burden of diseases.

2. Study objectives

We aimed to find association between VOC compounds and atopic dermatitis (AD) and asthma as well as estimate burden for the diseases. The detailed objects are:

(1) to compare the effects of AD and asthma by individual substance and mixtures at lower concentrations

(2) to identify the VOC groups and key substance that affect each disease and emission sources

(3) to estimate the burden of each disease attributed to VOC mixtures in terms of PAF and costs of illnesses

Ⅱ. LITERATURE REVIEW

1. Exposure of VOC and health effects

Exposure to VOCs occurs predominantly through inhalation, but dermal absorption and ingestion can also contribute [43-45]. The health effects of VOC exposure vary depending on the type, concentration, and duration of exposure [46]. Studies on individual VOC substances and their health effects in occupational, indoor, and outdoor exposures contexts are summarized in Table 1. Acute effects include eye, nose, skin irritation, fatigue, cardiovascular symptoms, and exacerbation of respiratory conditions such as asthma [18, 25-28, 34]. Chronic effects are more severe and include respiratory disorders, such as reduced lung function and chronic respiratory diseases, as well as hematologic impacts [24, 28, 29]. Individual exposure to particular VOCs, such as benzene and toluene, has also been associated with cardiovascular issues, likely due to systemic inflammation and arrhythmias [47]. Vulnerable populations such as children are particularly susceptible to these adverse effects [20, 21, 25, 28].

Additionally, studies have reported the relationship between VOCs and ozone (O_3), their secondary aerosol, in connection to respiratory diseases. Low ozone concentrations have been associated with increased wheeze incidence, likely due to the accumulation of hydrocarbons, which may act as airway irritants or sensitizers [25].

Table 1. Studies on individual exposure of VOCs and health effects

Reference	Place	Objective	Participants	Study Design	Pollutants	Biomarkers	Statistical methods	Short conclusions
Occuptational and indoor exposures								
[15]	hair salons, Taipei, Taiwan	cardio-vascular symptoms	62 hair dressing assistants (healthy, non-smokers, avg 25.2 yrs)	cross-sectional	VOCs	inflammation: serum CRP (blood), oxidative stress: 8-OHdG (blood), autonomic function: HRV (heart rate variability) index	mixed-effects regression	Exposure to VOCs was associated with increased serum CRP and increased 8-OHdG. HRV indices decreased with higher exposure to VOCs.
[16]	21 offices, Kaohsiung &Tainan, Taiwan	cardio-vascular symptoms	115 office workers	cross-sectional	tVOC, $PM_{2.5}$, CO_2, fungi, bacteria	SBP, DBP, HR	logistic regression, mixed effect model	Participants with higher BMI had elevated levels of SBP, DBP, and HR, especially when exposed to higher levels of tVOCs and fungi.
[17]	ship-building areas	oxidative stress, gene expression	shipbuilding workers (21 males, 29-53 yrs)	prospective cohort	BTEX	BTEX: MuA, HA, MaA, MHA (urine) oxidative stress: MDA, 8-OHdG gene expression: RNA samples (blood)	linear regression	Exposure to VOCs, particularly toluene, was associated with oxidative stress and changes in gene expression. Health risks linked to VOCs include respiratory, carcinogenic, reproductive, and neurological effects. However, the exact mechanisms of how VOCs cause these effects remain unclear.

Reference	Place	Objective	Participants	Study Design	Pollutants	Biomarkers	Statistical methods	Short conclusions
[18]	Hospital (14 wards, 49 rooms), Finland	respiratory and mucosal irritation, eye irritation, potentials for carcinogenic effects	470 hosptial employees	cross-sectional	2-ethyl-1-hexanol, aliphatic hydrocarbons, siloxanes	self-reported symptoms	linear regression	Hospital staff experienced a range of symptoms related to poor indoor air quality. Over 40% of respondents reported skin symptoms, 52% experienced nasal irritation and 25% reported headaches.
[19]	Canada, CHMS	lung function	general poplution (3039 non-smokers, 3-79 yrs)	cross-sectional, population-based (2009-2011)	84 VOCs	lung function: FEV1, FVC, FEV1/FVC	GLM	Increased concentrations of certain VOCs were associated with decreased lung function, particularly affecting children and young adults more than older adults.
[20]	Porto, Portugal, 73 classroom, 20 public primary school	respiratory symptoms, lung function	978 children (8-10 yrs)	cross-sectional	VOCs, aldehydes, PMs, CO_2, bacteria, fungi	lung function: FEV1, FVC, FEV1/FVC, FEF25-75%, FENO	logistic regression	Indoor pollutants, even at low levels, were significantly associated with an increased risk of respiratory symptoms such as wheezing, cough, phlegm, and nasal allergies. Higher exposure to $PM_{2.5}$, $PM_{10,}$ toluene, and acetaldehyde was linked to increased odds of wheezing.
[21]	Viseu, Portugal, non-industrial city	lung function	51 children	GEE	benzene, toluene, ethylbenzene, PM_{10}, NO_2, O_3	lung function: FENO, pH of EBC)	GEE	Increased levels of toluene, ethylbenzene and benzene exposure were linked to a higher need for medical intervention for wheezing.

Reference	Place	Objective	Participants	Study Design	Pollutants	Biomarkers	Statistical methods	Short conclusions
[22]	Perth, Australia	cardiovascular	111 adults (healthy, non-smokers, 65% women)	cross-sectional	formaldehyde, benzene, toluene, xylene, PAH	arterial stiffness (augmentation index, pulse wave velocity, central pulse pressure)	multiple linear regression	Higher indoor VOC concentrations were associated with increased arterial augmentation index (cAIx).
[23]	Taichung, Taiwan	atopic dermatitis	31 adults (20 cases, 11 control)	cross-sectional	VOCs	VOCs: BMA, DHBMA(urine)	multivariate linear regression	Patients with AD had elevated levels of metabolites of toluene (BMA) and 1,3-butadiene (DHBMA). These metabolites were associated with worsened AD symptoms, although the differences were not statistically significant after correcting for multiple comparisons. sources: paints, cleaning products, furnishings
[24]	Shanghai, China	hematologic	105 children with acute leukemia (15 yrs)	case-control	17 VOCs, NO_2	-	conditional logistic regression	Higher concentrations of NO_2 and several VOCs were associated with an increased risk of childhood acute leukemia(AL).
Outdoor exposure								
[25]	Lewisham, London, UK	wheezy episodes	children (<16 yrs) with wheezy episodes	prospective observational study (1995-1996)	hydrocarbons (benzene, propane, isoprene), O_3, NO_2, SO_2, PM_{10}	-	Poisson regression with dlm	Wheezy episodes: asthma, bronchiolitis, bronchospasm, wheezy bronhcitis. Low ozone concentrations were linked to increased wheeze incidence, likely due to the accumulation of hydrocarbons, which may act as airway irritants or sensitizers.

Reference	Place	Objective	Participants	Study Design	Pollutants	Biomarkers	Statistical methods	Short conclusions
[26]	Drammen, Oslo, Norway	respiratory diseases	patients with acute respiratory diseases	time-series (1994-1997)	benzene, toluene, formaldehyde, PM_{10}, NO_2, O_3, SO_2	-	Poisson regression	Benzene had a stronger association with respiratory hospital admissions compared to PM_{10}. Sources: motor vehicle emissions
[27]	Huntington Park, LA, USA	lung function	22 Hispanic children (10-16 yrs)	panel study (1999-2000)	VOCs, O_3, NO_2, SO_2, CO, PM_{10}, EC, OC	lung function: PEF	GEE, mixed effects regression	Asthma symptom severity & PEF, both symptoms and PEF were associated with exposure to VOCs and particulate pollutants, with VOCs showing significant associations with worsened asthma symptoms.
[28]	La Plata, Argentina, oil refininery and petero-chemical plants	lung function	1212 children (6-12 yrs)	cross-sectional	VOCs (benzene, toluene, xylene, hexane), PMs	FEV1, FVC, FEV1/FVC	multivariate logistic and linear regression	Children living near the petrochemical plants had significantly higher rates of asthma (24.8% compared to 10.1%-11.5% in other areas), more asthma exacerbations, and a greater prevalence of respiratory symptoms such as wheezing, dyspnea (difficulty breathing), nocturnal cough, and rhinitis. Children from the industrial regionals had lower lung function, with a 13% decrease in FEV1.

Reference	Place	Objective	Participants	Study Design	Pollutants	Biomarkers	Statistical methods	Short conclusions
[29]	USA, NHANES	respiratory disesases	12,386 participants (>=18 yrs)	cross-sectional (2003-2012)	VOCs	VOCs (blood)	logistic regression, GLM	Asthma, chronic bronchitis, emphysema, Certain blood VOC patterns, particularly pattern, were associated with an increased risk of these diseases.
[30]	Atlanta, Georgia, USA	respiratory and cardiovascular disesases	adults (>= 64 yrs)	time-series, case-crossover (1998-2006)	VOCs (alkanes, aromatics, microcrystalline oxides), transition metals, $PM_{2.5}$	-	two-stage hierarchical regression	Transition metals and alkanes were significantly associated with increased hospital admissions for CVD and respiratory diseases.
[31]	Taichung, Taiwan	cardiovascular disesases	general poplution	time-series (1993-2006)	VOCs, NO_2, CO, PM_{10}	-	GAM with Poisson	The study found significant associations between elevated levels of NO_2, CO, PM_{10}, and several VOCs (propane, iso- butane, and benzene) and increased risk of cardiovascular mortality, especially on the same day or with a lag of 1 to 2 days. Sources: traffic emissions
[32]	Strasbourg Metropolitan Area, France	cardiovascular disesases	participants (35-74 yrs)	case-crossover (2000-2007)	benzene, NO_2, PM_{10}, O_3, CO	-	conditional logistic regression	Increased benzene concentrations were significantly associated with the triggering of myocardial infarction(MI).

Reference	Place	Objective	Participants	Study Design	Pollutants	Biomarkers	Statistical methods	Short conclusions
[33]	Detroit, Michigan, USA (DEARS)	cardiovascular disesases	63 adults (19–80 yrs, non–smokers)	personal exposure, longitudinal observational study	VOCs	SBP, DBP, HR, BAD, FMD, NMD	PCA, linear mixed model	Butadiene–related VOCs were linked to decreases in DBP and increases in HR, while petroleum–related VOCs were associated with increases in FMD.
[9]	Kaohsiung City, Taiwan, industrial city	urticaria	adults (>=20 yrs), medical center visitor	case–crossover (2014–2018)	VOCs	– (IgE and eosinophil cationic protein levels were reviewed for patients with chronic or severe urticaria.)	conditional logistic regression	Higher levels of VOCs were associated with an increase in daily clinic visits for urticaria, suggesting a link between air pollution and the exacerbation of allergic skin conditions.
[34]	Kaohsiung City, Taiwan, industrial city	atopic dermatitis	patients with atopic dermatitis	case–crossover, NHIRD (2008–2018)	VOCs	–	conditional logistic regression, Poisson regression	Exposure to higher levels of ambient VOCs (1,3,5–trimethyl benzene and methylcyclohexane) was significantly associated with an increase in clinic visits for AD. Children were the most vulnerable subgroup, showing the highest odds of increased visits related to these VOCs.

Recent research has increasingly focused on the health effects of combined exposure to VOCs (Table 2). While studies primarily assess health effects attributed to mixed VOC exposures based on the concentrations of VOC metabolites, some have catergorized VOCs by their physical structure and investigated the relationship between VOC groups and cardiovascular and respiratory diseases [35, 48]. Despite significant progress, several research gaps remain. Comprehensive studies across diverse populations are needed, along with a deeper understanding of the adverse effects of VOC mixtures.

Table 2. Studies on combined exposure of VOCs and health effects

Reference	Place	Objective	Participants	Study Design	Pollutants	Biomarkers	Statistical methods	Short conclusions
[48]	Atlanta, USA	CVD, asthma	ED visitors with CVD and asthma	time-series (1998-2008)	VOCs (hydrocarbons, oxygenates)	-	Poisson regression: indicator pollutant approach, joint effect analysis, random effect meta-analysis	Hydrocarbon VOCs (especially alkenes and alkynes) were significantly associated with increased ED visits for CVD. Ketones were more strongly associated with increased ED visits for asthma, particularly in children.
[35]	Beijing, China	CVD	ED visitors with CVD, residents in Beijing >=6 month	time-series (2015-2016)	98 VOCs (hydrocarbons, oxygenates, halogenated)	-	GLM with Poisson, WQSR	*n*-alkanes, iso/anti-alkanes, aromatic, halogenated aromatic hydrocarbons, halogenated saturated chain hydrocarbons, and halogenated unsaturated chain hydrocarbons were associated with CVD emergency hospital admissions. Methylcyclohexane increased emergency admission risk by 8.68%. Styrene increased risk by 5.62%.
[36]	Wuhan, China	oxidative stress	1094 pregnant women	Cohort study (2014~2017)	VOCs	VOCs: urinary metabolites (GAMA, MU etc) oxidative stress: 8-OHdG, 8-OHG, HNEMA	LME, WQSR	Higher urinary concentrations of VOC metabolites were observed in early pregnancy and associated with increased oxidative stress biomarker levels. The VOC metabolite GAMA had the strongest association with DNA and RNA oxidation, while MU was most strongly linked to lipid peroxidation.

Reference	Place	Objective	Participants	Study Design	Pollutants	Biomarkers	Statistical methods	Short conclusions
[37]	12 cities, China	oxidative stress	205 particpants (16~78yrs)	cross-sectional	VOCs	VOCs: urinary metabolites oxidative stress: 8-OHdG, 8-OHG, diY	multiple linear regression, WQS, BKMR	VOC exposure was linked to oxidative damage affecting DNA, RNA, and proteins. High levels of specific VOC metabolites, such as crotonaldehyde and benzene, were associated with increased oxidative stress, suggesting potential health risks like respiratory and systemic inflammation.
[49]	USA, NHANES	all-cause mortality, cause-specific mortality (CVD,RD, cancer)	8799 participants (>=20yrs,150 4cases)	cross-sectional (2005~2018)	VOCs	VOCs: parents (acrolein, acrylonitirile, 1,3-butadiene, crotonaldehyde, *n,n*-dimethylformaldehyde, styrene, ethylbenzene etc), urinary metabolites (3-HPMA, DHBMA, MHBMA)	cox proportional hazard model, RCS model, ERS score from LASSO regression, PAF	All-cause mortality: 33.6% higher risk per 1-unit increase in Environment Risk Score (ERS). Cause-specific mortality: Increased risks for CVD (39.1%), RD(109.8%), and cancer(67.8%). PAFs: Joint VOC exposure contributed to 17.95% of all-cause deaths, 13.49% of CVD deaths, 35.65% of RD deaths, and 33.85% of cance rdeaths.
[50]	USA, NHANES	COPD	4983 participants	cross-sectional (2013~2016)	VOCs	VOCs: blood (Benzene,Toluene, 1,4-Dichlorobenzene, Tetrachloroethene, *o*-Xylene, *m/p*-Xylene, Chloroform, Bromodichloromethane) COPD: FEV1/FVC	weighted logistic regression, RCS, WQSR, machine learning models	Increased blood VOC concentrations (benzene, toluene, *o*-xylene, *m/p*-xylene) were significantly associated with higher odds of COPD. WQSR identified benzene and *o*-xylene as the most impactful contributors to COPD risk.

Reference	Place	Objective	Participants	Study Design	Pollutants	Biomarkers	Statistical methods	Short conclusions
[51]	USA, NHANES	COPD	5997 adults (>=20yrs)	cross-sectional (2011~2020)	VOCs	VOCs: urinary metabolites	multivariate logistic regression, BWQSR, Qgcomp,BKMR mediation analysis	Significant VOC metabolites(CEMA, CYMA, 3HPMA, MHBMA3, DHBMA) positively associated with COPD · BWQS: OR=1.30 (95%CI:1.06-1.58) per quartile increase · BKMR: Significant joint effect, with MHBMA3 and AMCC identified as top contributors · Qgcomp: OR=1.22 (95%CI: 0.98-1.52), marginally significant.
[38]	USA, NHANES	CVD	8468 participants (>=20yrs, 1504cases)	cross-sectional (2005~2018)	VOCs	VOCs: urinary metabolites	multivariate logistic regression, WQS, BKMR	Total urinary VOC concentrations were positively associated with CVD risk. VOC mixtures were significantly associated with CVD risks in both WQS and BKMR models.
[39]	USA, NHANES	liver injury, NAFLD	3011 adults (>=20yrs)	cross-sectional (2011~2016)	VOCs	VOCs: urinary metabolites liver function: ALT, AST, ALP etc NAFLD: USFLI	surveyed-weighted logistic regression, WQS, BKMR	Positive associations observed for certain VOC biomarkers with ALT, AST, ALP, and HFS. Negative associations observed with TBIL, ALB, and Total Protein.
[52]	USA, NHANES	diabetes mellitus	8468 participants (>=20yrs.1504cases)	cross-sectional (2005~2020)	VOCs	VOCs: urinary metabolites (CEMA, HPMA, DHBM, HPMM etc) glucose homeostasis: HbA1c, FPG, FINS, HOMA-IR	logistic regression, GLM WQS, Qgcomp	Odds ratios for diabetes ranged from 1.15 to 1.43 for individual VOC metabolites. VOC mixture effects (using WQS models): OR=1.52 (95%CI:1.29-1.81). Increased levels of VOCs correlated with worsened glucose homeostasis indicators.

Reference	Place	Objective	Participants	Study Design	Pollutants	Biomarkers	Statistical methods	Short conclusions
[40]	U S A , NHANES	MetS	8223 adults, 2001cases	cross-sectional (2005~2020)	VOCs	VOCs: urinary metabolites metabolic Syndrome: WC, TG, HDL-C, FBP, BP	GLM, RCS, WQS, BKMR	AMCC, CEMA, 3HPMA, and HMPMA were most strongly associated with MetS. CEMA had the highest contribution to MetS risk across multiple analyses (e.g.,WQS and BKMR models).
[29]	USA, NHANES	diabetes mellitus (DM), diateticretionpathy(DR)	2932 adults (>=20 yrs, 1466 cases)	cross-sectional (2011~2018)	VOCs	VOCs(22): blood (benzene, isopropylbenzene etc)	logistic regression, WQS, BKMR	Increased DM risk associated with 1,2-Dibromoethane, carbon tetrachloride, 2,5-dimethylfuran. Increased DR risk associated with 1,2-Dibromoethane, carbontetra-chloride, 2,5-dimethylfuran. Combined VOC exposure, analyzed via WQS regression, showed: OR=53.91 (95% CI: 34.11-85.22) for DM. OR=7.38 (95% CI: 3.65-14.92) for DR.
[53]	USA, NHANES	sleep health, depression	3473 participants (>=20 yrs, 618 cases)	cross-sectional (2005~2014)	VOCs	VOCs: urinary metabolites depression score: PHG-9	LASSO regression, PCA, WQS, BKMR, mediation analysis	WQSR indicated increased odds of poor sleep patterns, abnormal sleep duration, trouble sleeping, and sleep disorders. BKMR confirmed significant mixture effects of VOCs. Depression scores mediated 21.4-30.1% of the associations between VOC exposure and sleep outcomes.

2. Mechanism of atopic dermatitis development

Atopic dermatitis (AD) can arise from various factors, which are generally categorized into epidermal barrier dysfunction and immune system dysregulation. Air pollution poses considerable health risks and encompasses a diverse range of pollutants. Outdoor air pollutants, including particulate matter (PM), VOCs, gaseous substances, and heavy metals, have been associated with the occurrence of AD.

Pollutants trigger the activation of Th2 cells, leading to the downstream upregulation of various cytokines. This excessive cytokine activity promotes inflammation and IgE production, which are key contributors to the clinical features of AD. Since multiple environmental factors influence cytokine activity, targeting cytokine receptors presents a promising therapeutic approach [54].

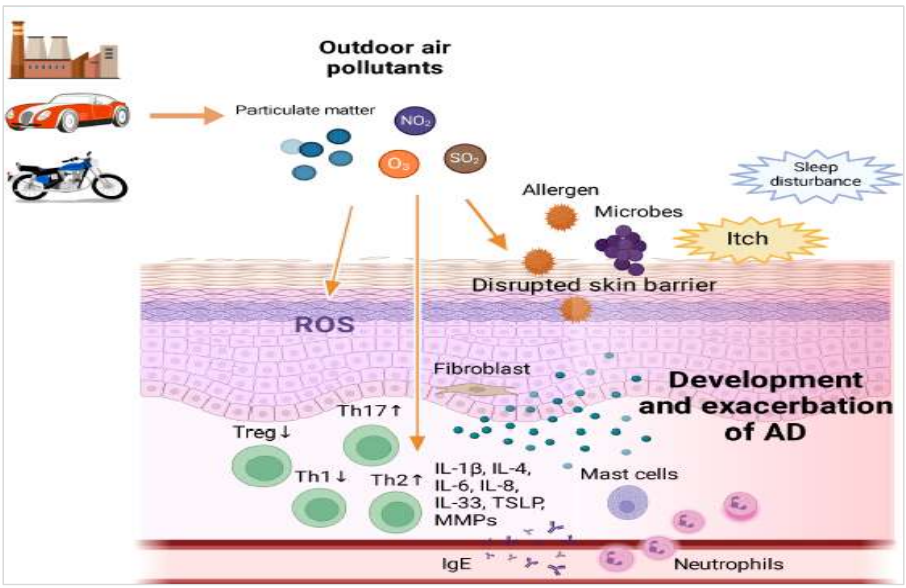


Figure 1. Mechanism of AD development by air pollutants [55]

3. Mechanism of asthma development

Exposure to VOCs has been identified as a significant factor in the development and exacerbation of asthma. VOCs enhance the polarization of Th2 cells, which are strongly associated with allergic inflammation and bronchial hyperreactivity. They also trigger inflammatory responses and oxidative stress in the lungs and respiratory tract, leading to impaired lung function and worsening asthma symptoms. Prenatal exposure to VOCs has been linked to alterations in neonatal T-cell cytokine secretion profiles, potentially increasing the risk of asthma and allergic diseases. Specific VOCs, such as benzene, toluene, and formaldehyde, are particularly toxic, contributing to inflammation, lung irritation, and immune system modulation, which are critical factors in the onset of asthma. Additionally, indoor air pollution caused by VOCs, particularly in poorly ventilated environments, poses a significant risk for asthma, especially in children [56].

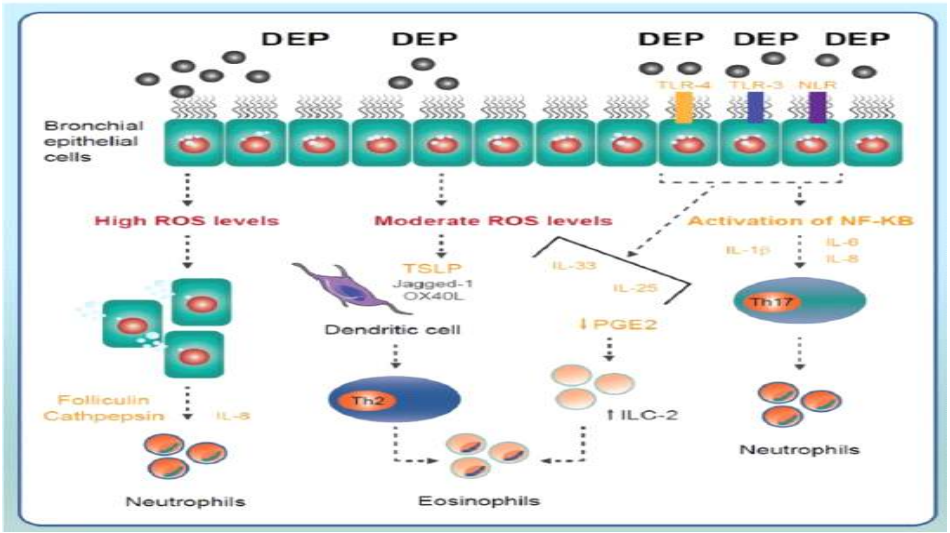


Figure 2. Mechanism of asthma development by air pollutants [57]

4. Health-related burden of diseases due to air pollutants

The methods of measuring the burden of diseases can be divided into three categories: using epidemiological indicators such as mortality or incidence rates, measuring from the perspective of economic burden, and finally, integrating disease states and mortality to represent the overall quality of life [58]. Domestic study on the health-related burden of diseases in terms of population attributable fraction (PAF) of air pollutants has been reported [59-61], which summarized in Table 3. However, the burden of AD and asthma caused by VOCs exposure still needs to be more studied.

Table 3. Domestic health-related burden of diseases results due to air pollutants [62]

Exposure	Health effect	ICD-10	PAF(%)	Population
Particulate matter (short-term)	non-accidental mortality	A00-R99	0.08	total population
	cardiovascular disease	I00-99	0.2 (onset) 0.1 (death)	
	IHD	I20-25	1.1 (onset) 0.1 (death)	
Particulate matter (long-term)	all-cause mortality	A00-Z99	12.4	>=30 yrs old
	lung cancer	C34	21.4 (death)	
	COPD	J40-44	20.3 (death)	
	stroke	I60-63, I65-67, I69.0-69.4, G45.8-9	42.2 (death) 37.3 (death) 32.5 (death) 27.4 (death) 21.9 (death) 13.7 (death)	30-39 yrs old 40-49 yrs old 50-59 yrs old 60-69 yrs old 70-79 yrs old >=80 yrs old
	IHD	I20-25	39.1 (death) 34.8 (death) 30.3 (death) 25.0 (death) 20.3 (death) 12.6 (death)	30-39 yrs old 40-49 yrs old 50-59 yrs old 60-69 yrs old 70-79 yrs old >=80 yrs old
Ozone	non-accidental mortality	A00-R99	0.03	total population

Ⅲ. MATERIALS AND METHODS

1. Study design

This research was based on time-series study that controlled variables such as long-term trends, seasonality, temperature, relative humidity, and holidays. First, we applied Generalized Additive Model (GAM) and Weighted Quantile Sum Regression (WQSR) models to evaluate the relationship between VOCs and health outcomes, comparing the effects of individual substance and mixture. Using Bayesian Kernel Machine Regression (BKMR), we evaluated the overall combined effects of total VOCs as well as group-specific combined effects and interactions within VOC groups that were significantly identified in WQS model. In addition, we calculated the health-related and economic burden of the diseases based on the VOC groups attributed to AD and asthma (Figure 3).

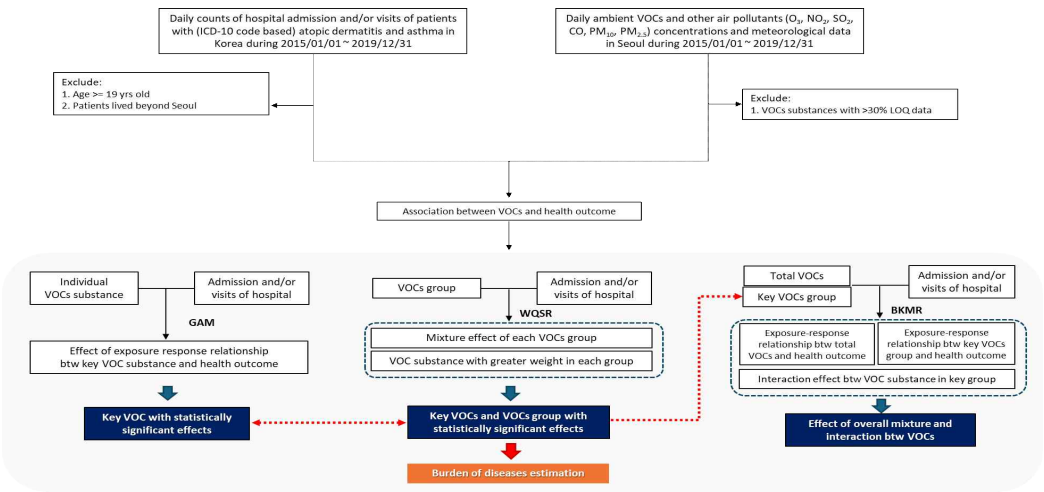


Figure 3. Flowchart of study design

2. Data sources

2-1) Medical use data

The data of daily hospital visits and/or admissions related to AD and asthma in Seoul between January 1, 2015, and December 31, 2019, was retrieved from National Health Insurance Service (NHIS) database. The surveillance system covers all medical institutions including primary health care facilities. This NHIS data covered about 2% of overall population in Korea and included information on medical use (diseases of ICD-10 code, days of hospitalization/visit, prescription, and medical practice), demographic variables (identification number, sex, birth year, death date, and residence area) as well as socio-economic variables (insurance premiums, and out-of-pocket payment).

Major allergic symptoms of cases were defined as follows: International Classification of Disease (ICD)-10 was used to identify AD and asthma (Table 4). The case data is represented by daily counts in each year of either first admission or second visit of hospital and/or clinic as the primary diagnosis. The daily counts with each disease were aggregated as a total (Table S1 and S2).

Table 4. ICD-10 code for allergic diseases

Major allergic diseases	ICD-10 code
Atopic dermatitis	L20.9
Asthma	J45.2 - J45.9, J46

2-2) VOCs data

The monitoring data for ambient VOCs was collected from the Seoul Government Research Institute of Public Health and Environment. The data includes monitoring stations with a detection rate of 70% or higher, comprising three automatic monitoring stations located in Gangseo-gu, Gwangjin-gu, and Jongro-gu in Seoul. Hourly data was collected from these mornitoring systems, which was then averaged to calculate daily mean values. Subsequently, the daily mean data was further averaged to obtain region-daily mean values.

In this study, we grouped ambient VOCs based on their chemical structures and estimated the effects of both individual substances and each group. The decision to group by chemical structure was driven by several factors: (1) Since chemical structure determines the reactivity of compounds, pollutants with similar chemical structures may exhibit similar toxicities. Grouping by chemical structure enhances the understanding of their health impacts from a biological perspective; and (2) Pollutants with the same chemical structure may originate from common emission sources or atmospheric chemical reactions. Grouping by chemical structure can therefore provide insights into the health effects of these sources or processes [48]. We further categorized the VOCs into four groups – *n*-Alkanes, branched or cyclo-Alkanes, Alkynes/Alkynes, and Aromatics – based on branching and molecular bonds [35]. The physico-chemical properties and toxicity classifications of each substance in VOC groups are presented in Table S3.

Table 5. VOC groups and individual substance

VOCs groups	Kinds	Substance
n-Alkanes	11	Ethane, Propane, *n*-Butane, *n*-Pentane, Hexane, *n*-Heptane, *n*-Octane, *n*-Nonane, *n*-Decane, *n*-Undecane, *n*-Dodecane
branched or cyclo-Alkanes	9	Isobutane, Isopentane, 2-Methylpentane, 3-Methylpentane, 3-Methylhexane, Cyclopentane, Cyclohexane, Methylcyclopentane, Methylcyclohexane,
Alkenes/Alkynes	4	Acetylene, Ethylene, Propylene, 1-Butene
Aromatics	6	Benzene, Ethylbenzene, Toluene, *m*/*p*-Xylene, *o*-Xylene, 1,2,4-Trimethylbenzene

2-3) Other Pollutants and Meteorological Conditions

Air pollution data, including ozone (O_3), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), carbon monoxide (CO), particulate matter with an aerodynamic diameter smaller than 10 ㎛ (PM_{10}), and particulate matter with an aerodynamic diameter smaller than 2.5 ㎛ ($PM_{2.5}$), was obtained from the Air Korea site (http://m.airkorea.or.kr/main). Daily measured data for meteorological variables, including temperature (℃), and relative humidity (%), was sourced from the Korea National Meteorological Administration (https://data.kma.go.kr/cmmn/main.do). Daily regional mean values were then calculated using the same methodology applied to the VOC data. The annual average concentration of air pollutants are presented in Table S4.

3. Statistical analysis

3-1) Exposure to ambient VOCs

After excluding VOC variables with more than 30% of values below the limit of quantification (LOQ) at each site, a total of 30 VOC substances were included in this study. The overall missing values for each VOC resulted from technical issues such as system or equipment failure, sample loss, or other unsatisfactory technicalities. To mitigate the potential inaccuracies caused by missing data, values missing due to technical issues were imputed using multiple imputation method [63]. LOQ-based missing values (0～29.8%) were replaced using the Half of Minimum (HM) method [64].

3-2) Generalized Additive Model (GAM)

The daily counts of AD and asthma cases in Seoul were assumed to follow a quasi-Poisson distribution to account for over-dispersion by relaxing the assumption that the variance equals the mean [65]. A generalized additive model (GAM) employing a quasi-Poisson distribution was utilized to assess the relative risk of hospital admissions or visits for each disease associated with individual substances within VOC groups. GAM is a semi-parametric model that combines linear and non-linear functions, providing flexibility in capturing complex relationships.

Temporal trends, temperature, relative humidity, day of the week, and public holidays were included as covariates in the main model to

control for potential confounding factors. A natural spline with 7 degrees of freedom (*df*) per year was used to control for time trends and temperature and relative humidity were modeled as natural spline functions with 6 and 3 *df*, respectively [66]. The model can be expressed as:

$$Log[E(Yt)] = \alpha + \beta VOCi + ns(date, df = 7/year) + ns(temperature, df = 6) + ns(humidity, df = 3) + DOW + holiday + log(offset)$$

Here, Y_t represents the number of hospital stays or visits on day t; β is the regression coefficient for a single substance estimated by the model; VOC_i denotes the concentration of the substance on day t; *ns* is a natural-spline function accounting for meteorological indicators and temporal trend; DOW is an indicator variable for the day of the week; and *holiday* represents an indicator variable for major public holidays. The total population of Seoul was also included as an *offset* term.

We also considered the lag effects of exposure for the same day (lag 0), as well as for subsequent days (lag 1, lag 2, lag 3, and lag 4). Additionally, we examined moving-average lag effects, including lag 01, lag 02, lag 03, and lag 04.

3-3) Weighted Quantile Sum Regression (WQSR) model

The Weghted Quantile Sum Regression (WQSR) model was used to estimate the association between exposure to VOC mixtures and each disease, with adjustments made to identify the important components of the chemical mixture. A WQS-based regression not only estimates the combined effect by constructing a weighted index but also explores the relative contributions of individual exposure substances to the combined effect. This is achieved through model allocation within various chemical structure categories, enabling the identification of key compounds that have a stronger impact on the outcome [35].

$$g(u) = \alpha + \beta_0 + \beta_1 \left(\sum_{i=1}^{c} w_i q_i \right) + z'\phi$$

$$WQS = \sum_{i=1}^{c} \overline{w_i} q_i$$

In this study, the weights were constrained to sum to 1 and lie between 0 and 1, thereby reducing dimensionality and addressing issues related to collinearity [67]. The WQSR index was calculated by dividing VOCs into quartiles. The data were randomly split into a training dataset (40%) and a validation dataset (60%), with the bootstrap set to 100 and repeated holdout set to 100. Both negative and positive WQSR indices (nWQSR and pWQSR) were initially examined to account for potential negative and positive associations. When no negative association was observed, only the positive index was used for the analysis [68]. A natural cubic spline with

6 degrees of freedom (*df*), 3 *df*, and 7 *df* per year was employed to adjust for the temperature, relative humidity and time trends, respectively. The results from the WQSR analyses were reported as Relative Risk (RR) and 95% Confidence Interval (CI) for the outcome associated with a quartile increase in the WQSR index.

3-4) Bayesian Kernel Machine Regression (BKMR) model

The Bayesian Kernel Machine Regression (BKMR) model was designed to address multivariable exposure-response functions in a flexible, non-parametric manner. This model is capable of selecting variables from exposed (potentially high-dimensional) vectors and identifying interactions and non-linearities among mixture components. It achieves this by incorporating grouping variable selection methods that adapt to highly correlated exposures [69].

The univariate exposure-response function of each VOC metabolite was visually represented to assess potential non-linearities in the exposure-response relationship. Additionally, bivariate exposure-response curves were used to visualize the interactions between mixture components. The slopes of the curves for a given chemical were evaluated at the 25th, 50th, and 75th percentiles of another chemical, while the remaining variables were fixed at the median. This approach highlighted possible interactions [70]. The BKMR model is:

$$Y_i = h(z_{i1}, \cdots, z_{iM}) + \beta x_i + \epsilon_i$$

Here, Y_i represents a continuous, normally distributed health endpoint, h

is a flexible function of the predictor variables z_{i1}, …, z_{iM}, and x_i is a vector of covariates. These covariates adjust for the following variables in this study: temperature (℃), relative humidity (%), date, day of the week (DOW), holiday and offset. The main idea of BKMR is to model exposure using a kernel function, and the number of iterations was set to 1,000, employing the MCMC (Markov Chain Monte Carlo) algorithm.

3-5) Statistical software

All descriptive statistics were performed using R software (Version 4.1.1, R Foundation for Statistical Computing, Vienna, Australia). Time-series analyses were conducted using the R packages 'splines', 'mgcv', and 'dlnm'. WQS regression and BKMR analyses were performed using the R packages 'gWQS' and 'bkmr', respectively. A p-value of <0.05 was considered statistically significant.

4. Burden of diseases estimates

4-1) Population Attributable Fraction (PAF)

To better quantify the burden of AD and asthma attributable to short-term exposure to ambient VOCs, the attributable number (AN) and poplulation attributable fraction (PAF) were applied. AN and PAF were calculated based on the concentration-response relationship obtained from the WQS regression analysis described above. The equations are shown below [6, 71, 72]:

$$AN = \sum_{i}^{n} (Baseline\ risk) * [\exp(\beta 0 * \Delta Ci) - 1]$$

$$PAF(\%) = \frac{Attributable\ number}{Total\ number} * 100$$

Here, *Baseline risk* refers to the average number of hospital admissions or visits on days with reference air pollution concentration; i represents days when the concentration exceeds the reference concentration; β_0 denotes the coefficients extracted from previous WQS model. $\triangle C_i$ represents the difference between the actual pollutant concentration and the reference pollutant concentration. *Total number* is the total counts of each disease during the study periods.

To date, no appropriate regulatory standards exist for controlling ambient VOC compounds, either internationally or domestically. In accordance with the World Health Organization (WHO)'s principles for

air quality standards, which recommends setting the minimum concentration associated with significant health effects as the criterion [73], we proposed three interim target scenarios by dividing the total concentrations of each statiscally significant VOC group into quartiles: Scenario 1, 2, and 3 were set at the 75th, 50th, and 25th percentiles of the total concentration levels, respectively. Assuming that reference concentration represents the minimum exposure concentration, it can be inferred that the number of patient cases occuring when the concentration exceeded the reference level is attributable to exposure to VOC exposure.

4-2) Economic burden of diseases

The economic burden of diseases was calculated using the following equations:

$$\text{(Total costs of diseases)} = \text{(Medical costs)} + \text{(Non-medical costs)}$$

$$\text{(Medical costs)} = \text{(Outpatient medical costs)} + \text{(Inpatient medical costs)} + \text{(Out-of-pocket costs)} + \text{(Drug costs)}$$

$$\text{(Non-medical costs)} = \text{(Transportation costs for hospital visits)}$$

Medical expenses were estimated using data from the NHIS database to determine disease-specific reimbursed medical costs. Transportation expenses were calculated by multiplying the number of inpatient stays or outpatient visits by the transportation cost per stay or visit. Pharmaceutical expenses for each disease were estimated under the assumption that the preferred primary treatment was administered at the

maximum dose for approximately one year across all age groups. The weighted average price of each main ingredient was calculated using medication information provided by the Health Insurance Review and Assessment Service (HIRA).

Table 6. Pharmaceuticals information used in children and adolescents

Diseases	Generic name	Dosage form	Initial dose/day
Atopic dermatitis	Steroid (topical)	Ointment	2 times/day, apply to the area
	Pimecrolimus	Ointment	2 times/day, apply to the area
	Tacrolimus	Tablet, Capsule	0.25~1 mg, 2 times/day
	Cyclosporine	Injection	25~100 mg/ 2 times/day
Asthma	Salbutamol	Inhaler	<12 yrs: 4 times/day, 1~2 spray/time >=12 yrs: 4~6 times/day, 1~2 spray/time
	Pranlukast	Tablet	5~50 mL

Subsequently, we calculated the total cost of diseases attributed to VOC compounds as described below.

$$AC_{y,medical} = AN_y \times C_{y,medical}$$
$$AC_{y,pocket} = AN_y \times C_{y,pocket}$$

Here, $AC_{y,total}$ represents the total medical costs resulting from exposure to VOC mixtures in year y, AN_y is the toal attributable number due to VOC compounds exceeding the reference concentration in year y; and $C_{y,medical}$ refers to the medical expenses in year y (per patient). $AC_{y,pocket}$ denotes the total out-of-pocket expenses attributable to VOC mixtures in year y.

5. Ethic statement

This study was approved by the Institutional Review Board, Yonsei University Health System (IRB number: 4-2024-1027) and was conducted with the tenets of the Declaration of Helsinki. The institutional review board waived the requirement for informed consent, as this was a retrospective study.

Ⅳ. RESULTS

1. Descriptive analysis

Throughout the study period between January 1, 2015 and December 31, 2019, a total of 469,546 hospital admissions or visits for AD and asthma were recorded in Seoul. The descriptive statistics for stays or visits to medical institutions for each disease, other air pollutants, and meteorological data are presented in Tables 7 and S5.

Table 7. Descriptive statistics of average daily cases, pollutants, and meteorological data in Seoul from 2015 to 2019

	Mean ± SD	Min	Q_1	Median	Q_3	IQR
Cases						
Atopic dermatitis	40 ± 20	0	34	44	53	19
Asthma	217 ± 109	15	143	219	287	144
Males	148 ± 71	10	106	152	194	88
Females	109 ± 54	5	77	113	144	67
0-2 yrs old	78 ± 46	2	46	71	103	57
3-6 yrs old	104 ± 49	8	73	107	136	63
7-12 yrs old	55 ± 29	1	37	56	73	36
13-18 yrs old	21 ± 12	0	14	22	28	14
Air pollutants						
VOCs (ppb)	34.0 ± 12.6	9.9	24.7	32.0	41.5	16.9
O_3 (ppb)	17.5 ± 7.3	4.0	12.1	16.4	21.7	9.6
NO_2 (ppb)	5.2 ± 1.8	1.6	3.9	4.9	6.2	2.4
SO_2 (ppb)	4.0 ± 1.6	1.3	2.7	3.7	4.9	2.2
CO (ppb)	7.4 ± 3.2	1.5	5.1	6.9	9.1	4.1
PM_{10} (μg/m^3)	23.9 ± 11.8	2.6	14.7	23.1	32.0	17.3
$PM_{2.5}$ (μg/m^3)	29.9 ± 11.6	7.2	21.0	27.9	37.7	16.7
Meteorological indicators						
Temperature (℃)	13.4 ± 10.8	-14.7	3.8	14.7	22.9	19.1
Relative humidity (%)	58.2 ± 14.7	18.3	47.2	58.5	68.2	21.1

SD: Standard deviation, Q_1: 25 percentiles, Q_3: 75 percentiles, IQR: Inter-quartile range

During the study period, the average daily numbers of AD and asthma case were 40 and 217. The average daily number of each disease was higher in male than female (males: 148, females: 109). The average daily concentrations of O_3, NO_2, SO_2, CO, PM_{10}, and $PM_{2.5}$ were 23.9 ppb, 29.9 ppb, 4.7 ppb, 518.7 ppb, 43.6 μg/m^3, and 24.3 μg/m^3, respectively. The average daily concentration of VOCs was 34.0 ± 12.6 ppb, with *n*-Alkanes constituting the largest prooportion (51.4%) at a daily average concentration of 17.5 ± 7.3 ppb. Aromatics accounted for the second highest proportion (21.7%) with a daily average concentration of 7.4 ± 3.2 ppb. Alkenes/Alkynes had the lowest proportion (11.7%), with an average daily concentration of 4.0 ± 1.6 ppb. The average daily concentrations for each group are presented in Figure 4. The correlation coefficients of substances within each VOC group are shown in Figure S6.

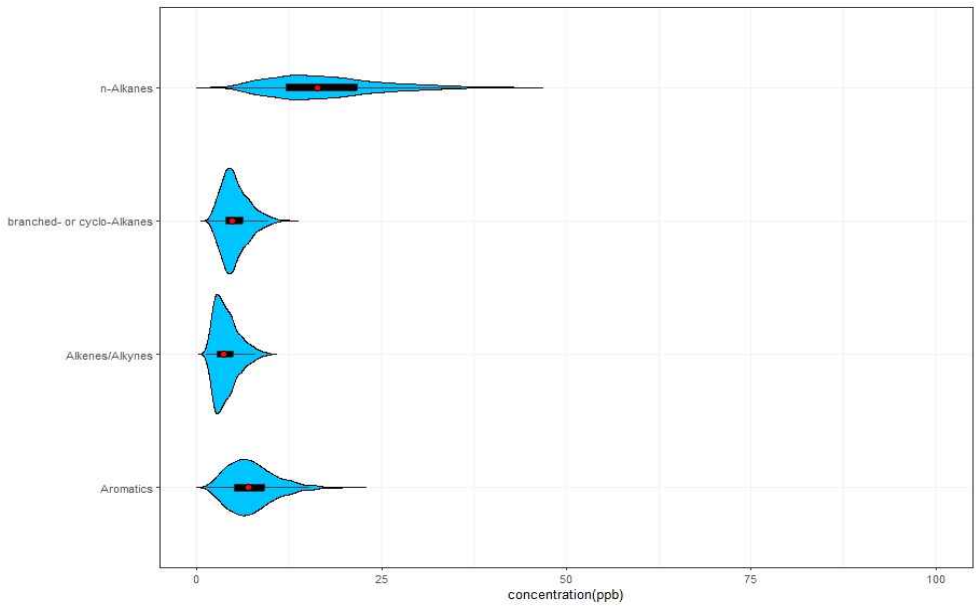


Figure 4. Violin plot of concentrations of VOC groups

2. Association between individual VOCs and medical institution admissions and visits for AD and asthma

2-1) Estimation of Relative Risk

We identified the relative risk of VOCs for AD and asthma per IQR increase in lag and moving-average lag days (Tables S6-9). Table 8 presents the significant associations between 23 VOCs and AD-related medical institution stays and visits.

In the *n*-Alkane group, the relative risks per IQR increases are observed for propane (lag 0), *n*-butane (lag 0), hexane (lag 4), *n*-heptane (lag 0), *n*-octane (lag 0), *n*-nonane (lag 0), *n*-decane (lag 0), *n*-undecane (lag 0), and *n*-dodecane (lag 4) as follows: 1.059 (95% CI: 1.019, 1.101), 1.050 (95% CI: 1.008, 1.094), 1.080 (95% CI: 1.043, 1.118), 1.028 (95% CI: 1.006, 1.051), 1.026 (95% CI: 1.005, 1.049), 1.036 (95% CI: 1.017, 1056), 1.037 (95% CI: 1.017, 1.058), 1.023 (95% CI: 1.004, 1.042), and 1.022 (95% CI: 1.001, 1.043), respectively. In the branched or cyclo-Alkanes group, the relative risks per IQR increase as follows: isopentane (lag 0), 1.042 (95% CI: 1.012, 1.073); 2-methylpentane (lag 0), 1.028 (95% CI: 1.001, 1.055); 3-methylhexane (lag 0), 1.036 (95% CI: 1.014, 1.058); cyclohexane (lag 4), 1.059 (95% CI: 1.032, 1.086); methylcyclopentane (lag 0), 1.077 (95% CI: 1.045, 1.110); and methylcyclohexane (lag 4) 1.046 (95% CI: 1.018, 1.074). In the Alkenes/Alkynes group, the relative risks per IQR increases for acetylene (lag 0), ethylene (lag 0), and propylene (lag 0) are 1.047 (95% CI: 1.006, 1.090), 1.049 (95% CI: 1.006, 1.094), and 1.044 (95% CI: 1.005, 1.084), respectively. In the Aromatics group, the relative risks per IQR

increases for benzene (lag 0), ethylbenzene (lag 0), toluene (lag 4), *o*-xylene (lag 0), and 1,2,4-trimethylbenzene (lag 0) are 1.059 (95% CI: 1.012, 1.108), 1.041 (95% CI: 1.014, 1.069), 1.090 (95% CI: 1.057, 1.123), 1.030 (95% CI: 1.001, 1.060), and 1.036 (95% CI: 1.014, 1.058), respectively.

Table 8. Relative risk (95% CI) of medical institution admissions and visits for AD per IQR[a] increment for key VOCs

VOCs groups	Key substance	Lag[b]	RR (95% CI)
n-Alkanes	Propane	lag 0	1.059 (1.019, 1.101)
	n-Butane	lag 0	1.050 (1.008, 1.094)
	Hexane	lag 4	1.080 (1.043, 1.118)
	n-Heptane	lag 0	1.028 (1.006, 1.051)
	n-Octane	lag 0	1.026 (1.005, 1.049)
	n-Nonane	lag 0	1.036 (1.017, 1.056)
	n-Decane	lag 0	1.037 (1.017, 1.058)
	n-Undecane	lag 0	1.023 (1.004, 1.042)
	n-Dodecane	lag 4	1.022 (1.001, 1.043)
branched or cyclo-Alkanes	Isopentane	lag 0	1.042 (1.012, 1.073)
	2-Methylpentane	lag 0	1.028 (1.001, 1.055)
	3-Methylhexane	lag 0	1.036 (1.014, 1.058)
	Cyclohexane	lag 4	1.059 (1.032, 1.086)
	Methylcyclopentane	lag 0	1.077 (1.045, 1.110)
	Methylcyclohexane	lag 4	1.046 (1.018, 1.074)
Alkenes/Alkynes	Acetylene	lag 0	1.047 (1.006, 1.090)
	Ethylene	lag 0	1.049 (1.006, 1.094)
	Propylene	lag 0	1.044 (1.005, 1.084)
Aromatics	Benzene	lag 0	1.059 (1.012, 1.108)
	Ethylbenzene	lag 0	1.041 (1.014, 1.069)
	Toluene	lag 4	1.090 (1.057, 1.123)
	o-Xylene	lag 0	1.030 (1.001, 1.060)
	1,2,4-Trimethylbenzene	lag 0	1.036 (1.014, 1.058)

[a]IQR values are shown in the Table S5; [b]Lag day with the highest RR are selected from the Table S6 and S7.

Table 9 presents the significant associations between 14 VOCs and medical institution stays and visits for asthma. In the n-Alkane group, the relative risks per IQR increases are observed for propane (lag 0), *n*-butane (lag 4), *n*-pentane (lag 04), hexane (lag 4), *n*-heptane (lag 4), *n*-decane (lag 0), and *n*-dodecane (lag 4) as follows: 1.036 (95% CI: 1.004, 1.069), 1.036 (95% CI: 1.002, 1.072), 1.051 (95% CI: 1.006, 1.098), 1.068 (95% CI: 1.038, 1.098), 1.024 (95% CI: 1.006, 1.042), 1.019 (95% CI: 1.002, 1035), and 1.023 (95% CI: 1.006, 1.040), respectively. In the branched or cyclo-Alkanes group, the relative risks per IQR increase as follows: 2-methylpentane (lag 4), 1.027 (95% CI: 1.004, 1.050); 3-methylhexane (lag 04), 1.044 (95% CI: 1.008, 1.081); cyclohexane (lag 4), 1.048 (95% CI: 1.028, 1.070); methylcyclopentane (lag 0), 1.060 (95% CI: 1.034, 1.086); and methylcyclohexane (lag 4) 1.039 (95% CI: 1.017, 1.061). In the Aromatics group, the relative risks per IQR increases for ethylbenzene (lag 4) and toluene (lag 4) are 1.023 (95% CI: 1.003, 1.043) and 1.070 (95% CI: 1.045, 1.095), respectively.

Table 9. Relative risk (95% CI) of medical institution admissions and visits for asthma per IQR[a] increment for key VOCs

VOCs groups	Key substance	Lag[b]	RR (95% CI)
n-Alkanes	Propane	lag 0	1.036 (1.004, 1.069)
	n-Butane	lag 4	1.036 (1.002, 1.072)
	n-Pentane	lag 04	1.051 (1.006, 1.098)
	Hexane	lag 4	1.068 (1.038, 1.098)
	n-Heptane	lag 4	1.024 (1.006, 1.042)
	n-Decane	lag 0	1.019 (1.002, 1.035)
	n-Dodecane	lag 4	1.023 (1.006, 1.040)
branched or cyclo-Alkanes	2-Methylpentane	lag 4	1.027 (1.004, 1.050)
	3-Methylhexane	lag 04	1.044 (1.008, 1.081)
	Cyclohexane	lag 4	1.048 (1.028, 1.070)
	Methylcyclopentane	lag 0	1.060 (1.034, 1.086)
	Methylcyclohexane	lag 4	1.039 (1.017, 1.061)
Aromatics	Ethylbenzene	lag 4	1.023 (1.003, 1.043)
	Toluene	lag 4	1.070 (1.045, 1.095)

[a]IQR values are shown in the Table S5; [b]Lag day with the highest RR are selected from the Table S8 and S9.

2-2) Sub-group analysis

The results of the stratified analysis by sex are listed in Tables 10 and 11. For AD, the effects of propane (lag 0), *n*-butane (lag 0), *n*-heptane (lag 0), *n*-octane (lag 0), *n*-nonane (lag 0), *n*-decane (lag 0), isopentane (lag 0), 2-methylpentane (lag 0), methylcyclopentane (lag 0), acetylene (lag 0), ethylene (lag 0), ethylbenzene (lag 0), and *o*-xylene (lag 0) were greater in females than in males. Conversely, the effects of hexane (lag 4), *n*-undecane (lag 0), *n*-dodecane (lag 4), cyclohexane (lag 4), methylcyclohexane (lag 4), benzene (lag 0), and toluene (lag 4) were greater in males than in females. However, the differences between sexes were not significant for any of the key VOCs.

For asthma, the effects of *n*-butane (lag 4), 3-methylhexane (lag 04), and toluene (lag 4) were greater in females than in males. Conversely, the effects of hexane (lag 4), *n*-heptane (lag 4), *n*-decane (lag 0), *n*-dodecane (lag 4), 2-methylpentane (lag 4), methylcyclohexane (lag 0), methylcyclohexane (lag 4), and ethylbenzene (lag 4), the effects were greater in males than in females. However, the differences between sexes were not significant for any of the key VOCs.

Table 10. Association between VOC exposure and medical institution admissions and visits for AD by sex

VOC groups	Key substance	RR (95% CI) by sex		*p*-value for interaction
		Male	Female	
n-Alkanes	Propane (at lag 0)	1.068 (1.026, 1.112)*	1.048 (1.005, 1.094)*	0.533
	n-Butane (at lag 0)	1.060 (1.015, 1.106)*	1.038 (0.992, 1.085)	0.511
	Hexane (at lag 4)	1.077 (1.038, 1.117)*	1.084 (1.043, 1.126)*	0.809
	n-Heptane (at lag 0)	1.032 (1.009, 1.056)*	1.023 (0.999, 1.048)	0.583
	n-Octane (at lag 0)	1.027 (1.004, 1.050)*	1.026 (1.002, 1.051)*	0.968
	n-Nonane (at lag 0)	1.037 (1.017, 1.058)*	1.035 (1.014, 1.057)*	0.909
	n-Decane (at lag 0)	1.038 (1.017, 1.059)*	1.036 (1.014, 1.059)*	0.924
	n-Undecane (at lag 0)	1.022 (1.002, 1.042)*	1.025 (1.004, 1.046)*	0.838
	n-Dodecane (at lag 4)	1.019 (0.997, 1.041)	1.026 (1.003, 1.049)*	0.677
branchedor cyclo-Alkanes	Isopentane (at lag 0)	1.047 (1.015, 1.079)*	1.036 (1.003, 1.071)*	0.667
	2-Methylpentane (at lag 0)	1.033 (1.005, 1.062)*	1.020 (0.991, 1.050)	0.529
	3-Methylhexane (at lag 0)	1.036 (1.013, 1.059)*	1.036 (1.012, 1.060)*	0.998
	Cyclohexane (at lag 4)	1.054 (1.026, 1.082)*	1.065 (1.036, 1.095)*	0.575
	Methylcyclopentane (at lag 0)	1.078 (1.044, 1.113)*	1.075 (1.040, 1.112)*	0.916
	Methylcyclohexane (at lag 4)	1.040 (1.012, 1.070)*	1.053 (1.023, 1.084)*	0.567
Alkenes/Alkynes	Acetylene (at lag 0)	1.054 (1.011, 1.100)*	1.038 (0.992, 1.085)	0.606
	Ethylene (at lag 0)	1.061 (1.016, 1.109)*	1.034 (0.987, 1.082)	0.418
	Propylene (at lag 0)	1.044 (1.003, 1.085)*	1.044 (1.002, 1.088)*	0.982
Aromatics	Benzene (at lag 0)	1.057 (1.009, 1.109)*	1.061 (1.010, 1.115)*	0.924
	Ethylbenzene (at lag 0)	1.047 (1.018, 1.076)*	1.035 (1.005, 1.065)*	0.582
	Toluene (at lag 4)	1.081 (1.048, 1.116)*	1.101 (1.065, 1.138)*	0.445
	o-Xylene (at lag 0)	1.035 (1.005, 1.067)*	1.023 (0.991, 1.055)	0.586
	1,2,4-Trimethylbenzene (at lag 0)	1.036 (1.013, 1.059)*	1.036 (1.012, 1.060)*	0.987

*p-value <0.05: statistically significant

Table 11. Association between VOC exposure and medical institution admissions and visits for asthma by sex

VOC groups	Key substance	RR (95% CI) by sex		*p*-value for interaction
		Male	Female	
n-Alkanes	Propane (at lag 0)	1.036 (1.003, 1.070)*	1.036 (1.003, 1.070)*	0.997
	n-Butane (at lag 4)	1.040 (1.005, 1.077)*	1.031 (0.996, 1.067)	0.711
	n-Pentane (at lag 04)	1.051 (1.005, 1.098)*	1.051 (1.005, 1.099)*	0.998
	Hexane (at lag 4)	1.067 (1.037, 1.098)*	1.069 (1.039, 1.100)*	0.919
	n-Heptane (at lag 4)	1.022 (1.003, 1.040)*	1.026 (1.008, 1.045)*	0.726
	n-Decane (at lag 0)	1.017 (1.001, 1.034)*	1.021 (1.004, 1.038)*	0.728
	n-Dodecane (at lag 4)	1.021 (1.004, 1.039)*	1.025 (1.007, 1.043)*	0.762
branched or cyclo-Alkanes	2-Methylpentane (at lag 4)	1.026 (1.003, 1.049)*	1.028 (1.005, 1.052)*	0.887
	3-Methylhexane (at lag 04)	1.048 (1.011, 1.085)*	1.040 (1.003, 1.078)*	0.773
	Cyclohexane (at lag 4)	1.048 (1.027, 1.070)*	1.048 (1.027, 1.070)*	0.988
	Methylcyclopentane (at lag 0)	1.059 (1.033, 1.085)*	1.062 (1.036, 1.089)*	0.862
	Methylcyclohexane (at lag 4)	1.037 (1.015, 1.060)*	1.040 (1.018, 1.063)*	0.864
Aromatics	Ethylbenzene (at lag 4)	1.021 (1.001, 1.042)*	1.025 (1.004, 1.046)*	0.781
	Toluene (at lag 4)	1.072 (1.046, 1.098)*	1.067 (1.041, 1.093)*	0.813

*p-value <0.05: statistically significant

For the age group-stratified analysis, the associations between exposure to different VOCs and medical institutions stays and visits for AD and asthma are presented (Tables 10 and 11).

For AD, the age group with the highest relative risks for key substances was 3-6 years. The effects of propane (lag 0), *n*-butane (lag 0), *n*-decane (lag 0), *n*-undecane (lag 0), 2-methylpentane (lag 0), 3-methylhexane (lag 0), and methylcyclopentane (lag 0) were highest in the 0-2 age group. The effects of *n*-octane (lag 0), *n*-nonane (lag 0), *n*-decane (lag 0), isopentane (lag 0), 2-methylpentane (lag 0), acetylene (lag 0), ethylene (lag 0), and propylene (lag 0) were highest in the 3-6 age group. For the 7-12 age group, the effects of propane (lag 0), *n*-butane (lag 0), hexane (lag 4), methylcyclohexane (lag 4), and toluene (lag 4) were highest. In the 13-18 age group, the effects of *n*-dodecane (lag 4), cyclohexane (lag 4), benzene (lag 0), ethylbenzene (lag 0), *o*-xylene (lag 0), and 1,2,4-trimethylbenzene (lag 0) were highest. However, the differences between age groups were not significant for any of the key VOCs.

For asthma, the age group with the highest relative risks for key substances was 13-18 years, while the age group with the most statistically significant substances was 0-2 years. The effects of *n*-pentane (lag 04), *n*-dodecane (lag 4), and 3-methylhexane (lag 04) were highest in the 0-2 age group. The effects of *n*-butane (lag 4), *n*-decane (lag 0), and toluene (lag 4) were highest in the 3-6 age group. For the 7-12 age group, the effect of methylcyclopentane (lag 0) was highest. In the 13-18 age group, the effects of propane (lag 0), hexane (lag 4), *n*-heptane (lag 4), 2-methylpentane (lag 4), cyclohexane (lag 4), methylcyclohexane (lag 4), and ethylbenzene (lag 4) were highest. However, the differences between age groups were not significant for any of the key VOCs.

Table 12. Association between VOCs exposure and medical institution admissions and visits for AD by age groups

VOC groups	Key substance	RR (95% CI) by age groups				*p*-value for interaction
		<3 yrs	3~6 yrs	7~12 yrs	13~18 yrs	
n-Alkanes	Propane (at lag 0)	1.062 (1.018, 1.109)*	1.053 (1.008, 1.100)*	1.062 (1.012, 1.114)*	1.061 (1.005, 1.120)*	0.991
	n-Butane (at lag 0)	1.060 (1.013, 1.109)*	1.044 (0.997, 1.093)	1.060 (1.008, 1.115)*	1.031 (0.974, 1.092)	0.865
	Hexane (at lag 4)	1.060 (1.020, 1.101)*	1.081 (1.039, 1.125)*	1.093 (1.046, 1.141)*	1.087 (1.035, 1.143)*	0.731
	n-Heptane (at lag 0)	1.028 (1.004, 1.052)*	1.024 (0.999, 1.049)	1.028 (1.000, 1.055)	1.036 (1.005, 1.068)*	0.946
	n-Octane (at lag 0)	1.019 (0.995, 1.043)	1.036 (1.011, 1.062)*	1.023 (0.996, 1.051)	1.027 (0.996, 1.060)	0.795
	n-Nonane (at lag 0)	1.028 (1.007, 1.049)*	1.041 (1.019, 1.064)*	1.038 (1.014, 1.062)*	1.037 (1.010, 1.065)*	0.859
	n-Decane (at lag 0)	1.039 (1.017, 1.061)*	1.039 (1.016, 1.062)*	1.033 (1.009, 1.059)*	1.036 (1.008, 1.066)*	0.989
	n-Undecane (at lag 0)	1.025 (1.005, 1.046)*	1.022 (1.001, 1.044)*	1.022 (0.999, 1.046)	1.021 (0.993, 1.049)	0.994
	n-Dodecane (at lag 4)	1.021 (0.999, 1.043)	1.016 (0.992, 1.040)	1.021 (0.995, 1.048)	1.034 (1.005, 1.064)*	0.815
branched or cyclo-Alkanes	Isopentane (at lag 0)	1.040 (1.007, 1.074)*	1.050 (1.016, 1.086)*	1.036 (0.999, 1.075)	1.041 (0.999, 1.085)	0.958
	2-Methylpentane (at lag 0)	1.032 (1.003, 1.062)*	1.032 (1.002, 1.064)*	1.021 (0.988, 1.055)	1.023 (0.986, 1.061)	0.947
	3-Methylhexane (at lag 0)	1.041 (1.017, 1.065)*	1.037 (1.012, 1.062)*	1.027 (1.000, 1.054)	1.039 (1.009, 1.070)*	0.888
	Cyclohexane (at lag 4)	1.041 (1.012, 1.070)*	1.062 (1.032, 1.093)*	1.065 (1.032, 1.099)*	1.068 (1.031, 1.107)*	0.608
	Methylcyclopentane (at lag 0)	1.087 (1.051, 1.125)*	1.075 (1.039, 1.113)*	1.071 (1.031, 1.113)*	1.074 (1.028, 1.121)*	0.939
	Methylcyclohexane (at lag 4)	1.042 (1.012, 1.073)*	1.042 (1.011, 1.074)*	1.056 (1.022, 1.091)*	1.039 (1.002, 1.079)*	0.913

VOC groups	Key substance	RR (95% CI) by age groups				*p*-value for interaction
		<3 yrs	3~6 yrs	7~12 yrs	13~18 yrs	
Alkenes/ Alkynes	Acetylene (at lag 0)	1.038 (0.992, 1.085)	1.060 (1.012, 1.109)*	1.054 (1.002, 1.108)*	1.027 (0.970, 1.088)	0.826
	Ethylene (at lag 0)	1.026 (0.979, 1.075)	1.060 (1.011, 1.111)*	1.052 (0.999, 1.108)	1.056 (0.995, 1.119)	0.775
	Propylene (at lag 0)	1.035 (0.993, 1.078)	1.049 (1.005, 1.094)*	1.039 (0.991, 1.088)	1.053 (0.999, 1.110)	0.949
Aromatics	Benzene (at lag 0)	1.049 (1.000, 1.102)	1.066 (1.013, 1.123)*	1.041 (0.983, 1.101)	1.085 (1.018, 1.157)*	0.771
	Ethylbenzene (at lag 0)	1.041 (1.012, 1.072)*	1.037 (1.007, 1.069)*	1.031 (0.998, 1.065)	1.063 (1.025, 1.103)*	0.654
	Toluene (at lag 4)	1.067 (1.032, 1.103)*	1.090 (1.053, 1.128)*	1.107 (1.066, 1.149)*	1.095 (1.049, 1.144)*	0.535
	o-Xylene (at lag 0)	1.022 (0.991, 1.055)	1.023 (0.990, 1.057)	1.031 (0.994, 1.068)	1.049 (1.008, 1.092)*	0.755
	1,2,4-Trimethylbenzene (at lag 4)	1.027 (1.003, 1.050)*	1.040 (1.016, 1.065)*	1.035 (1.008, 1.062)*	1.042 (1.012, 1.073)*	0.831

*p-value <0.05: statistically significant

Table 13. Association between VOCs exposure and medical institution admissions and visits for asthma by age groups

VOC groups	Key substance	RR (95% CI) by age groups				*p*-value for interaction
		<3 yrs	3~6 yrs	7~12 yrs	13~18 yrs	
n-Alkanes	Propane (at lag 0)	1.038 (1.004, 1.072)*	1.038 (1.005, 1.072)*	1.026 (0.987, 1.065)	1.049 (1.004, 1.096)*	0.896
	n-Butane (at lag 4)	1.037 (1.002, 1.074)*	1.041 (1.005, 1.077)*	1.036 (0.994, 1.079)	1.015 (0.968, 1.063)	0.848
	n-Pentane (at lag 04)	1.087 (1.040, 1.136)*	1.039 (0.993, 1.087)	1.030 (0.977, 1.087)	1.008 (0.948, 1.072)	0.197
	Hexane (at lag 4)	1.072 (1.041, 1.104)*	1.063 (1.033, 1.094)*	1.071 (1.035, 1.108)*	1.086 (1.044, 1.130)*	0.865
	n-Heptane (at lag 4)	1.027 (1.008, 1.045)*	1.022 (1.004, 1.041)*	1.019 (0.998, 1.041)	1.037 (1.012, 1.063)*	0.730
	n-Decane (at lag 0)	1.019 (1.002, 1.036)*	1.022 (1.006, 1.039)*	1.013 (0.993, 1.033)	1.014 (0.991, 1.037)	0.893
	n-Dodecane (at lag 4)	1.026 (1.008, 1.044)*	1.022 (1.004, 1.040)*	1.023 (1.002, 1.044)*	1.020 (0.996, 1.045)	0.984
branched or cyclo-Alkanes	2-Methylpentane (at lag 4)	1.028 (1.005, 1.051)*	1.028 (1.005, 1.052)*	1.021 (0.994, 1.049)	1.033 (1.002, 1.065)*	0.951
	3-Methylhexane (at lag 04)	1.063 (1.026, 1.102)*	1.041 (1.004, 1.078)*	1.037 (0.994, 1.081)	1.001 (0.953, 1.052)	0.289
	Cyclohexane (at lag 4)	1.050 (1.028, 1.072)*	1.047 (1.025, 1.069)*	1.046 (1.021, 1.072)*	1.057 (1.027, 1.087)*	0.949
	Methylcyclopentane (at lag 0)	1.064 (1.038, 1.092)*	1.054 (1.028, 1.081)*	1.071 (1.039, 1.103)*	1.044 (1.008, 1.080)*	0.679
	Methylcyclohexane (at lag 4)	1.042 (1.020, 1.065)*	1.034 (1.012, 1.057)*	1.037 (1.011, 1.064)*	1.047 (1.017, 1.078)*	0.916
Aromatics	Ethylbenzene (at lag 4)	1.021 (1.001, 1.042)*	1.024 (1.003, 1.045)*	1.021 (0.997, 1.046)	1.030 (1.001, 1.059)*	0.970
	Toluene (at lag 4)	1.064 (1.039, 1.090)*	1.074 (1.048, 1.100)*	1.071 (1.040, 1.102)*	1.070 (1.034, 1.108)*	0.964

*p-value <0.05: statistically significant

The results of the stratified analysis by seasons are listed in Tables 14 and 15.

For AD, the season with the highest relative risk for key substance was spring, while the seasons with the most statistically significant substances were spring and summer. The effects of hexane (lag 4), *n*-decane (lag 0), cyclohexane (lag 4), methylcyclopentane (lag 0), ethylbenzene (lag 0), and toluene (lag 4) were highest in spring. The effects of *n*-nonane (lag 0), methylcyclohexane (lag 4), ethylene (lag 0), and 1,2,4-trimethylbenzene (lag 0) were highest in summer. During autumn, the effect of 3-methylhexane (lag 0) was the highest. The differences between seasons were statistically significant for 3-methylhexane (p-value for interaction <0.05).

For asthma, the season with the highest relative risk for key substances was also spring. The effects of 2-methylpentane (lag 4), cyclohexane (lag 4), methylcyclopentane (lag 0), and toluene (lag 4) were the highest in spring. The effects of hexane (lag 4) and *n*-heptane (lag 4) were highest in summer. However, the differences between seasons are not statistically significant for any of the key VOCs.

Table 14. Association between VOCs exposure and medical institution admissions and visits for AD by seasons

VOC groups	Key substance	RR (95% CI) by seasons				*p*-value for interaction
		Spring	Summer	Autumn	Winter	
n-Alkanes	Propane (at lag 0)	1.057 (0.964, 1.159)	1.108 (0.992, 1.237)	1.079 (0.989, 1.177)	1.011 (0.942, 1.086)	0.499
	n-Butane (at lag 0)	1.102 (0.998, 1.216)	1.064 (0.971, 1.165)	0.998 (0.911, 1.094)	1.020 (0.932, 1.115)	0.475
	Hexane (at lag 4)	1.097 (1.018, 1.182)*	1.165 (1.063, 1.277)*	1.061 (0.981, 1.148)	1.028 (0.958, 1.103)	0.182
	n-Heptane (at lag 0)	1.016 (0.957, 1.079)	1.031 (0.981, 1.084)	1.020 (0.979, 1.063)	1.026 (0.978, 1.076)	0.982
	n-Octane (at lag 0)	1.022 (0.976, 1.070)	1.027 (0.983, 1.072)	1.003 (0.951, 1.058)	1.044 (0.997, 1.094)	0.736
	n-Nonane (at lag 0)	1.047 (0.999, 1.096)	1.062 (1.005, 1.121)*	1.029 (0.990, 1.069)	1.021 (0.986, 1.056)	0.614
	n-Decane (at lag 0)	1.050 (1.004, 1.098)*	1.022 (0.968, 1.079)	1.040 (0.997, 1.086)	1.032 (0.995, 1.070)	0.881
	n-Undecane (at lag 0)	1.029 (0.992, 1.068)	1.026 (0.982, 1.072)	1.004 (0.963, 1.047)	1.034 (0.992, 1.077)	0.773
	n-Dodecane (at lag 4)	1.016 (0.976, 1.057)	1.021 (0.976, 1.069)	1.023 (0.975, 1.073)	1.038 (0.985, 1.094)	0.937
branched or cyclo-Alkanes	Isopentane (at lag 0)	1.044 (0.980, 1.113)	1.056 (0.985, 1.132)	1.010 (0.942, 1.082)	1.049 (0.984, 1.118)	0.806
	2-Methylpentane (at lag 0)	1.029 (0.963, 1.100)	1.028 (0.982, 1.076)	1.042 (0.977, 1.111)	1.006 (0.944, 1.072)	0.896
	3-Methylhexane (at lag 4)	0.996 (0.949, 1.045)	1.053 (0.998, 1.112)	1.091 (1.039, 1.145)*	1.003 (0.965, 1.043)	0.021**
	Cyclohexane (at lag 4)	1.078 (1.023, 1.137)*	1.074 (1.007, 1.145)*	1.069 (1.008, 1.134)*	1.009 (0.960, 1.060)	0.240
	Methylcyclopentane (at lag 4)	1.103 (1.030, 1.180)*	1.065 (0.979, 1.159)	1.090 (1.024, 1.160)*	1.020 (0.954, 1.090)	0.373
	Methylcyclohexane (at lag 4)	1.039 (0.984, 1.096)	1.079 (1.010, 1.153)*	1.078 (1.013, 1.146)*	0.981 (0.927, 1.038)	0.087

VOC groups	Key substance	RR (95% CI) by seasons				*p*-value for interaction
		Spring	Summer	Autumn	Winter	
Alkenes/ Alkynes	Acetylene (at lag 0)	1.072 (0.978, 1.176)	0.999 (0.883, 1.130)	1.050 (0.943, 1.169)	1.040 (0.975, 1.110)	0.840
	Ethylene (at lag 0)	1.069 (0.971, 1.178)	1.145 (1.002, 1.309)*	1.012 (0.916, 1.117)	0.998 (0.929, 1.071)	0.274
	Propylene (at lag 0)	1.060 (0.962, 1.169)	1.031 (0.958, 1.108)	1.047 (0.960, 1.143)	1.010 (0.934, 1.092)	0.875
Aromatics	Benzene (at lag 0)	1.001 (0.908, 1.102)	1.128 (0.986, 1.291)	1.053 (0.946, 1.172)	1.039 (0.957, 1.127)	0.564
	Ethylbenzene (at lag 0)	1.074 (1.008, 1.144)*	1.066 (0.995, 1.142)	1.008 (0.956, 1.063)	1.025 (0.973, 1.080)	0.380
	Toluene (at lag 4)	1.146 (1.064, 1.233)*	1.127 (1.044, 1.217)*	1.087 (1.021, 1.157)*	1.037 (0.979, 1.098)	0.146
	o-Xylene (at lag 0)	1.066 (0.987, 1.151)	1.064 (0.990, 1.143)	0.999 (0.950, 1.052)	1.029 (0.964, 1.100)	0.410
	1,2,4-Trimethylbenzene (at lag 4)	1.052 (1.006, 1.100)*	1.082 (1.004, 1.166)*	1.013 (0.970, 1.059)	1.029 (0.989, 1.071)	0.413

*p-value <0.05: statistically significant
** p-value for interaction <0.05: statistically significant

Table 15. Association between VOCs exposure and medical institution admissions and visits for asthma by seasons

VOC groups	Key substance	RR (95% CI) by seasons				*p*-value for interaction
		Spring	Summer	Autumn	Winter	
n-Alkanes	Propane (at lag 0)	1.043 (0.971, 1.121)	1.083 (0.990, 1.184)	1.047 (0.980, 1.119)	0.981 (0.922, 1.044)	0.273
	n-Butane (at lag 4)	1.074 (0.996, 1.158)	1.077 (0.998, 1.162)	1.053 (0.982, 1.129)	0.981 (0.915, 1.050)	0.220
	n-Pentane (at lag 04)	1.049 (0.941, 1.169)	0.991 (0.884, 1.112)	0.997 (0.895, 1.110)	1.034 (0.936 1143)	0.864
	Hexane (at lag 4)	1.082 (1.022, 1.145)*	1.126 (1.047, 1.211)*	1.054 (0.993, 1.120)	1.056 (0.994, 1.121)	0.504
	n-Heptane (at lag 4)	1.041 (0.996, 1.088)	1.063 (1.014, 1.114)*	1.021 (0.990, 1.053)	0.985 (0.943, 1.029)	0.110
	n-Decane (at lag 0)	1.031 (0.996, 1.068)	1.031 (0.988, 1.075)	1.022 (0.989, 1.056)	1.002 (0.969, 1.037)	0.638
	n-Dodecane (at lag 4)	1.024 (0.994, 1.055)	1.012 (0.975, 1.049)	1.035 (0.998, 1.073)	1.031 (0.981, 1.084)	0.789
branched or cyclo-Alkanes	2-Methylpentane (at lag 4)	1.050 (1.001, 1.102)*	1.023 (0.985, 1.063)	1.043 (0.993, 1.095)	0.988 (0.936, 1.043)	0.363
	3-Methylhexane (at lag 04)	1.002 (0.915, 1.098)	0.992 (0.896, 1.098)	1.006 (0.930, 1.087)	1.031 (0.948, 1.122)	0.941
	Cyclohexane (at lag 4)	1.074 (1.031, 1.118)*	1.057 (1.003, 1.113)*	1.042 (0.997, 1.088)	1.018 (0.976, 1.060)	0.322
	Methylcyclopentane (at lag 0)	1.085 (1.030, 1.143)*	1.057 (0.988, 1.130)	1.062 (1.013, 1.113)*	0.990 (0.934, 1.049)	0.126
	Methylcyclohexane (at lag 4)	1.037 (0.995, 1.080)	1.050 (0.996, 1.108)	1.054 (1.008, 1.103)*	1.007 (0.961, 1.056)	0.532
Aromatics	Ethylbenzene (at lag 4)	1.035 (0.990, 1.082)	1.027 (0.972, 1.084)	1.013 (0.973, 1.054)	1.016 (0.976, 1.057)	0.889
	Toluene (at lag 4)	1.114 (1.054, 1.177)*	1.079 (1.016, 1.146)*	1.048 (1.002, 1.097)*	1.062 (1.012, 1.114)*	0.392

*p-value <0.05: statistically significant

The results of the stratified analysis by sites are listed in Tables 16 and 17.

For AD, the site with the highest relative risk for key substances was site 3. The effect of benzene (lag 0) was highest in site 1. The effects of *n*-undecane (lag 0), isopentane (lag 0), cyclohexane (lag 4), methylcyclohexane (lag 4), acetylene (lag 0), and toluene (lag 4) were highest in site 2. In site 3, the effects of hexane (lag 4), *n*-heptane (lag 0), *n*-octane (lag 0), *n*-nonane (lag 0), *n*-decane (lag 0), 3-methylhexane (lag 0), methylcyclopentane (lag 0), ethylene (lag 0), propylene (lag 0), benzene (lag 0), ethylbenzene (lag0), *o*-xylene (lag 0), and 1,2,4-trimethylbenzne (lag 0) were the highest. The differences between sites were statistically significant for *n*-heptane and *n*-nonane (*p*-value for interaction <0.05).

For asthma, the site with the highest relative risk for key substances was site 3. The effect of hexane (lag 4) was highest in site 1. The effects of *n*-pentane (lag 04), *n*-decane (lag 0), and 3-methylhexane (lag 04) were highest in site 2. In site 3, the effects of *n*-heptane (lag 4), *n*-dodecane (lag 4), cyclohexane (lag 4), methylcyclopentane (lag 0), methylcyclohexane (lag 4), ethylbenzene (lag 4), and toluene (lag 4) were the highest. However, the differences between sites were not statistically significant for any of the key VOCs.

Table 16. Association between VOCs exposure and medical institution admissions and visits for AD by sites

VOC groups	Key substance	RR (95% CI) by sites			*p*-value for interaction
		Site 1	Site 2	Site 3	
n-Alkanes	Propane (at lag 0)	1.013 (0.984, 1.042)	1.030 (0.999, 1.062)	1.033 (0.999, 1.069)	0.610
	n-Butane (at lag 0)	1.019 (0.994, 1.043)	1.032 (0.988, 1.078)	0.992 (0.952, 1.034)	0.410
	Hexane (at lag 4)	1.049 (1.017, 1.081)*	1.026 (1.004, 1.047)*	1.054 (1.016, 1.095)*	0.317
	n-Heptane (at lag 0)	1.017 (0.995, 1.040)	1.003 (0.993, 1.014)	1.039 (1.017, 1.062)*	0.015**
	n-Octane (at lag 0)	1.008 (0.996, 1.020)	1.006 (0.989, 1.024)	1.039 (1.011, 1.068)*	0.113
	n-Nonane (at lag 0)	1.015 (1.004, 1.027)*	1.013 (1.000, 1.025)	1.064 (1.034, 1.096)*	0.007**
	n-Decane (at lag 0)	1.015 (1.004, 1.026)*	1.017 (1.004, 1.031)*	1.037 (1.001, 1.074)*	0.520
	n-Undecane (at lag 0)	1.010 (0.999, 1.022)	1.028 (1.008, 1.048)*	1.003 (0.990, 1.017)	0.140
	n-Dodecane (at lag 4)	1.010 (0.997, 1.024)	1.010 (0.995, 1.025)	1.015 (0.999, 1.030)	0.903
branched or cyclo-Alkanes	Isopentane (at lag 0)	1.024 (0.997, 1.052)	1.022 (1.003, 1.042)*	1.010 (0.986, 1.035)	0.690
	2-Methylpentane (at lag 0)	1.010 (0.988, 1.033)	1.006 (0.992, 1.021)	1.015 (0.989, 1.042)	0.840
	3-Methylhexane (at lag 4)	1.009 (0.988, 1.030)	1.010 (0.998, 1.022)	1.030 (1.011, 1.048)*	0.185
	Cyclohexane (at lag 4)	1.018 (0.999, 1.038)	1.029 (1.011, 1.048)*	1.046 (1.020, 1.072)*	0.248
	Methylcyclopentane (at lag 4)	1.032 (1.013, 1.052)*	1.029 (1.004, 1.055)*	1.038 (1.009, 1.068)*	0.902
	Methylcyclohexane (at lag 4)	1.011 (0.994, 1.029)	1.032 (1.011, 1.054)*	1.019 (0.994, 1.044)	0.332

VOC groups	Key substance	RR (95% CI) by sites			*p*-value for interaction
		Site 1	Site 2	Site 3	
Alkenes/ Alkynes	Acetylene (at lag 0)	1.004 (0.975, 1.035)	1.039 (1.002, 1.077)*	1.025 (0.999, 1.052)	0.340
	Ethylene (at lag 0)	1.009 (0.966, 1.053)	1.009 (0.972, 1.046)	1.034 (1.006, 1.063)*	0.456
	Propylene (at lag 0)	1.012 (0.986, 1.039)	1.010 (0.983, 1.037)	1.045 (1.011, 1.080)*	0.233
Aromatics	Benzene (at lag 0)	1.043 (1.003, 1.085)*	1.018 (0.986, 1.050)	1.043 (1.003, 1.084)*	0.516
	Ethylbenzene (at lag 0)	1.015 (0.999, 1.031)	1.012 (0.986, 1.039)	1.038 (1.007, 1.070)*	0.372
	Toluene (at lag 4)	1.039 (1.014, 1.066)*	1.057 (1.029, 1.086)*	1.052 (1.026, 1.079)*	0.645
	o-Xylene (at lag 0)	1.019 (1.001, 1.039)*	0.998 (0.980, 1.017)	1.042 (1.006, 1.079)*	0.068
	1,2,4-Trimethylbenzene (at lag 4)	1.012 (1.002, 1.022)*	1.022 (0.993, 1.052)	1.051 (1.016, 1.087)*	0.100

*p-value <0.05: statistically significant;
** p-value for interaction <0.05: statistically significant

Table 17. Association between VOCs exposure and medical institution admissions and visits for asthma by sites

VOC groups	Key substance	RR (95% CI) by sites			*p*-value for interaction
		Site 1	Site 2	Site 3	
n-Alkanes	Propane (at lag 0)	1.018 (0.999, 1.039)	1.016 (0.991, 1.041)	1.018 (0.992, 1.044)	0.985
	n-Butane (at lag 4)	1.017 (1.000, 1.035)	1.026 (0.992, 1.060)	1.007 (0.977, 1.039)	0.728
	n-Pentane (at lag 04)	1.017 (0.982, 1.053)	1.034 (1.006, 1.064)*	1.014 (0.982, 1.048)	0.622
	Hexane (at lag 4)	1.039 (1.017, 1.061)*	1.011 (0.996, 1.028)	1.060 (1.030, 1.092)*	0.010
	n-Heptane (at lag 4)	1.000 (0.986, 1.015)	1.006 (0.998, 1.014)	1.027 (1.009, 1.044)*	0.062
	n-Decane (at lag 0)	1.004 (0.996, 1.011)	1.013 (1.003, 1.024)*	1.024 (0.996, 1.052)	0.171
	n-Dodecane (at lag 4)	1.000 (0.990, 1.009)	1.014 (1.003, 1.025)*	1.017 (1.005, 1.030)*	0.049**
branched or cyclo-Alkanes	2-Methylpentane (at lag 4)	1.008 (0.993, 1.024)	1.003 (0.992, 1.015)	1.018 (0.998, 1.039)	0.466
	3-Methylhexane (at lag 04)	0.994 (0.969, 1.020)	1.026 (1.006, 1.046)*	1.028 (1.000, 1.057)	0.118
	Cyclohexane (at lag 4)	1.007 (0.994, 1.019)	1.022 (1.009, 1.036)*	1.049 (1.029, 1.069)*	0.002**
	Methylcyclopentane (at lag 0)	1.022 (1.009, 1.035)*	1.025 (1.006, 1.044)*	1.033 (1.010, 1.056)*	0.722
	Methylcyclohexane (at lag 4)	1.004 (0.993, 1.016)	1.023 (1.007, 1.039)*	1.034 (1.014, 1.054)*	0.022**
Aromatics	Ethylbenzene (at lag 4)	1.004 (0.994, 1.015)	1.014 (0.997, 1.031)	1.041 (1.018, 1.065)*	0.017**
	Toluene (at lag 4)	1.019 (1.003, 1.036)*	1.038 (1.017, 1.059)*	1.051 (1.031, 1.071)*	0.055

*p-value <0.05: statistically significant
** p-value for interaction <0.05: statistically significant

2-3) Sensitivity analysis

The results obtained after adjusting for different air pollutants in the model are shown in Tables 18 and 19.

For AD, while the relative risks for most VOCs decreased after adjusting for different air pollutants compared to the main models, the relative risks remained comparable and increased for hexane (lag 4), *n*-dodecane (lag 4), cyclohexane (lag 4), methylcyclohexane (lag 4), and toluene (lag 4).

For asthma, although the associations between most VOCs and asthma were inconsistent after adjusting for different air pollutants compared to the main model, the overall relative risks remained comparable and decreased for propane (lag 0) and *n*-decane (lag 0). They remained comparable and increased for hexane (lag 4). For *n*-pentane (lag 04), the relative risks increased after adjusting for O_3, NO_2, CO, PM_{10}, and $PM_{2.5}$, but decreased after SO_2 adjustment. For 3-methylhexane (lag 04), the relative risks increased after adjusting for O_3, NO_2, and CO but decreased after SO_2 adjustment. For Methylcyclopentane (lag 0), the relative risks increased after adjusting for NO_2 and CO but decreased after PM_{10}, and $PM_{2.5}$ adjustments.

Table 18. Relative risk (95% CI) in medical institution admissions and visits for AD per IQR increment for key VOCs after adjusting for air pollutants

VOC groups	Key substance	adjust for O_3	adjust for NO_2	adjust for SO_2	adjust for CO	adjust for PM_{10}	adjust for $PM_{2.5}$
n-Alkanes	Propane (at lag0)	1.051 (1.010, 1.095)*	1.023 (0.976, 1.073)	1.047 (1.005, 1.091)*	1.046 (1.000, 1.094)	1.052 (1.011, 1.094)*	1.052 (1.011, 1.096)*
	n-Butane (at lag0)	1.041 (0.998, 1.086)	1.018 (0.972, 1.066)	1.038 (0.995, 1.084)	1.035 (0.990, 1.083)	1.042 (1.000, 1.086)	1.044 (1.001, 1.088)*
	Hexane (at lag4)	1.081 (1.044, 1.119)*	1.086 (1.048, 1.124)*	1.080 (1.043, 1.118)*	1.083 (1.046, 1.121)*	1.082 (1.045, 1.120)*	1.080 (1.044, 1.119)*
	n-Heptane (at lag0)	1.025 (1.002, 1.048)*	1.011 (0.986, 1.036)	1.021 (0.998, 1.045)	1.020 (0.996, 1.045)	1.024 (1.002, 1.047)*	1.024 (1.001, 1.047)*
	n-Octane (at lag0)	1.023 (1.001, 1.046)*	1.011 (0.986, 1.035)	1.020 (0.997, 1.043)	1.019 (0.995, 1.043)	1.020 (0.998, 1.043)	1.022 (1.000, 1.045)
	n-Nonane (at lag0)	1.034 (1.014, 1.054)*	1.028 (1.007, 1.049)*	1.033 (1.013, 1.053)*	1.033 (1.012, 1.053)*	1.033 (1.013, 1.053)*	1.034 (1.014, 1.054)*
	n-Decane (at lag0)	1.034 (1.014, 1.055)*	1.028 (1.007, 1.050)*	1.033 (1.013, 1.054)*	1.033 (1.012, 1.054)*	1.034 (1.014, 1.055)*	1.035 (1.015, 1.056)*
	n-Undecane (at lag0)	1.021 (1.002, 1.041)*	1.017 (0.998, 1.037)	1.020 (1.001, 1.040)*	1.020 (1.001, 1.040)*	1.021 (1.002, 1.040)*	1.021 (1.002, 1.041)*
	n-Dodecane (at lag4)	1.022 (1.001, 1.043)*	1.024 (1.003, 1.045)*	1.022 (1.001, 1.043)*	1.023 (1.002, 1.044)*	1.022 (1.002, 1.043)*	1.022 (1.001, 1.043)*
branched or cyclo-Alkanes	Isopentane (at lag 0)	1.036 (1.005, 1.068)*	1.013 (0.977, 1.050)	1.032 (1.000, 1.065)	1.031 (0.996, 1.066)	1.036 (1.005, 1.067)*	1.037 (1.006, 1.069)*
	2-Methylpentane (at lag 0)	1.024 (0.997, 1.051)	1.012 (0.983, 1.041)	1.022 (0.995, 1.050)	1.020 (0.992, 1.049)	1.024 (0.997, 1.052)	1.025 (0.998, 1.052)
	3-Methylhexane (at lag 0)	1.030 (1.008, 1.052)*	1.020 (0.996, 1.045)	1.029 (1.007, 1.052)*	1.028 (1.004, 1.052)*	1.032 (1.011, 1.055)*	1.032 (1.010, 1.054)*
	Cyclohexane (at lag 4)	1.059 (1.033, 1.086)*	1.061 (1.035, 1.088)*	1.059 (1.032, 1.086)*	1.060 (1.033, 1.087)*	1.059 (1.032, 1.086)*	1.059 (1.032, 1.086)*
	Methylcyclopentane (at lag 0)	1.052 (1.022, 1.083)*	1.062 (1.026, 1.100)*	1.070 (1.035, 1.106)*	1.071 (1.036, 1.108)*	1.071 (1.038, 1.104)*	1.072 (1.038, 1.106)*
	Methylcyclohexane (at lag 4)	1.046 (1.019, 1.074)*	1.048 (1.020, 1.076)*	1.046 (1.018, 1.073)*	1.046 (1.019, 1.074)*	1.046 (1.019, 1.074)*	1.046 (1.018, 1.074)*

VOC groups	Key substance	adjust for O_3	adjust for NO_2	adjust for SO_2	adjust for CO	adjust for PM_{10}	adjust for $PM_{2.5}$
Alkenes/ Alkynes	Acetylene (at lag 0)	1.041 (0.999, 1.084)	1.019 (0.974, 1.065)	1.037 (0.994, 1.081)	1.032 (0.987, 1.079)	1.038 (0.997, 1.082)	1.040 (0.997, 1.084)
	Ethylene (at lag 0)	1.039 (0.993, 1.086)	1.001 (0.948, 1.056)	1.034 (0.988, 1.081)	1.028 (0.977, 1.083)	1.039 (0.996, 1.084)	1.038 (0.993, 1.085)
	Propylene (at lag 0)	1.037 (0.998, 1.078)	1.019 (0.977, 1.062)	1.034 (0.995, 1.075)	1.032 (0.991, 1.075)	1.038 (1.000, 1.078)	1.038 (0.999, 1.079)
Aromatics	Benzene (at lag0)	1.056 (1.009, 1.105)*	1.023 (0.972, 1.076)	1.036 (0.985, 1.090)	1.033 (0.979, 1.090)	1.043 (0.995, 1.092)	1.042 (0.991, 1.096)
	Ethylbenzene (at lag0)	1.037 (1.009, 1.066)*	1.020 (0.990, 1.052)	1.034 (1.006, 1.063)*	1.032 (1.003, 1.063)*	1.036 (1.009, 1.064)*	1.037 (1.009, 1.065)*
	Toluene (at lag4)	1.090 (1.058, 1.124)*	1.092 (1.060, 1.126)*	1.089 (1.056, 1.122)*	1.091 (1.059, 1.125)*	1.090 (1.057, 1.123)*	1.088 (1.056, 1.122)*
	o-Xylene (at lag0)	1.024 (0.995, 1.055)	1.010 (0.979, 1.042)	1.022 (0.992, 1.053)	1.021 (0.990, 1.052)	1.025 (0.996, 1.055)	1.025 (0.995, 1.055)
	1,2,4-Trimethylbenzene (at lag0)	1.033 (1.012, 1.055)*	1.026 (1.004, 1.049)*	1.032 (1.010, 1.054)*	1.032 (1.009, 1.054)*	1.033 (1.011, 1.055)*	1.033 (1.011, 1.055)*

*p-value <0.05: statistically significant

Table 19. Relative risk (95% CI) in medical institution admissions and visits for asthma per IQR increment for key VOCs after adjusting for air pollutants

VOC groups	Key substance	adjust for O_3	adjust for NO_2	adjust for SO_2	adjust for CO	adjust for PM_{10}	adjust for $PM_{2.5}$
n-Alkanes	Propane (at lag 0)	1.034 (1.000, 1.069)	1.030 (0.990, 1.071)	1.032 (0.998, 1.068)	1.037 (0.999, 1.076)	1.033 (1.001, 1.067)*	1.034 (1.000, 1.068)
	n-Butane (at lag 4)	1.036 (1.002, 1.072)*	1.037 (1.003, 1.073)*	1.036 (1.002, 1.072)*	1.037 (1.002, 1.072)*	1.037 (1.003, 1.073)*	1.037 (1.002, 1.072)*
	n-Pentane (at lag 04)	1.057 (1.011, 1.106)*	1.061 (1.005, 1.121)*	1.036 (0.986, 1.088)	1.055 (1.002, 1.111)*	1.055 (1.008, 1.105)*	1.055 (1.008, 1.105)*
	Hexane (at lag 4)	1.068 (1.039, 1.099)*	1.071 (1.041, 1.101)*	1.068 (1.038, 1.098)*	1.070 (1.040, 1.100)*	1.069 (1.039, 1.099)*	1.068 (1.038, 1.099)*
	n-Heptane (at lag 4)	1.024 (1.006, 1.042)*	1.024 (1.006, 1.043)*	1.024 (1.006, 1.042)*	1.024 (1.006, 1.042)*	1.024 (1.006, 1.042)*	1.024 (1.006, 1.042)*
	n-Decane (at lag 0)	1.018 (1.001, 1.035)*	1.016 (0.998, 1.033)	1.017 (1.000, 1.034)	1.017 (1.000, 1.035)	1.018 (1.001, 1.034)*	1.018 (1.001, 1.034)*
	n-Dodecane (at lag 4)	1.023 (1.006, 1.041)*	1.024 (1.006, 1.041)*	1.023 (1.006, 1.040)*	1.023 (1.006, 1.041)*	1.023 (1.006, 1.041)*	1.023 (1.006, 1.041)*
branched or cyclo-Alkanes	2-Methylpentane (at lag 4)	1.027 (1.004, 1.050)*	1.027 (1.005, 1.050)*	1.027 (1.004, 1.050)*	1.027 (1.004, 1.050)*	1.027 (1.004, 1.050)*	1.027 (1.004, 1.050)*
	3-Methylhexane (at lag 04)	1.049 (1.012, 1.087)*	1.051 (1.008, 1.095)*	1.035 (0.997, 1.074)	1.047 (1.006, 1.089)*	1.045 (1.009, 1.083)*	1.045 (1.009, 1.083)*
	Cyclohexane (at lag 4)	1.049 (1.028, 1.070)*	1.049 (1.028, 1.071)*	1.048 (1.028, 1.070)*	1.049 (1.028, 1.070)*	1.048 (1.027, 1.070)*	1.048 (1.027, 1.070)*
	Methylcyclopentane (at lag 0)	1.061 (1.034, 1.088)*	1.062 (1.032, 1.092)*	1.059 (1.031, 1.087)*	1.062 (1.033, 1.091)*	1.057 (1.031, 1.084)*	1.058 (1.031, 1.085)*
	Methylcyclohexane (at lag 4)	1.039 (1.017, 1.061)*	1.040 (1.018, 1.062)*	1.039 (1.017, 1.061)*	1.039 (1.017, 1.061)*	1.039 (1.017, 1.061)*	1.039 (1.017, 1.061)*
Aromatics	Ethylbenzene (at lag 4)	1.023 (1.003, 1.043)*	1.023 (1.003, 1.044)*	1.023 (1.002, 1.043)*	1.023 (1.003, 1.043)*	1.023 (1.003, 1.043)*	1.023 (1.003, 1.043)*
	Toluene (at lag 4)	1.070 (1.045, 1.096)*	1.071 (1.046, 1.097)*	1.069 (1.044, 1.095)*	1.071 (1.046, 1.096)*	1.069 (1.044, 1.095)*	1.069 (1.044, 1.094)*

*p-value <0.05: statistically significant

3. Association between VOC mixtures and medical institution admissions and visits for AD and asthma using WQSR model

3-1) Estimation of Relative Risk

Figure 5 demonstrates the combined effect of a quartile increase in the WQS index for each VOC group on medical institution admissions and visits for AD and asthma. The relative risk per quartile increase in the WQS index for branched or cyclo-Alkanes was associated with AD-related medical institutaion stays and visits, with a value of 1.048 (95% CI: 1.028, 1.068) at lag 0. No significant associations were observed between other VOC groups (*n*-Alkanes, Alkenes/Alkynes, and aromatics) and AD-related medical institutions stays and visits for AD at lag 0.

For asthma, the relative risks per quartile increase in the WQS index for branched or cyclo-Alkanes was 1.033 (95% CI: 1.013, 1.053) at lag 0. No significant associations were observed between other VOC groups and asthma-related medical institutions stays and visits at lag 0.

We calculated the moving-average lag effects (Tables S10 and S11). For AD, the relative risk for branched or cyclo-Alkanes at lag 0 was the only statistically significant result. The results showed that the acute effects of VOCs on asthma decreased over time and increased again from lag 02 or lag 03, but no significant associations was observed beyond that.

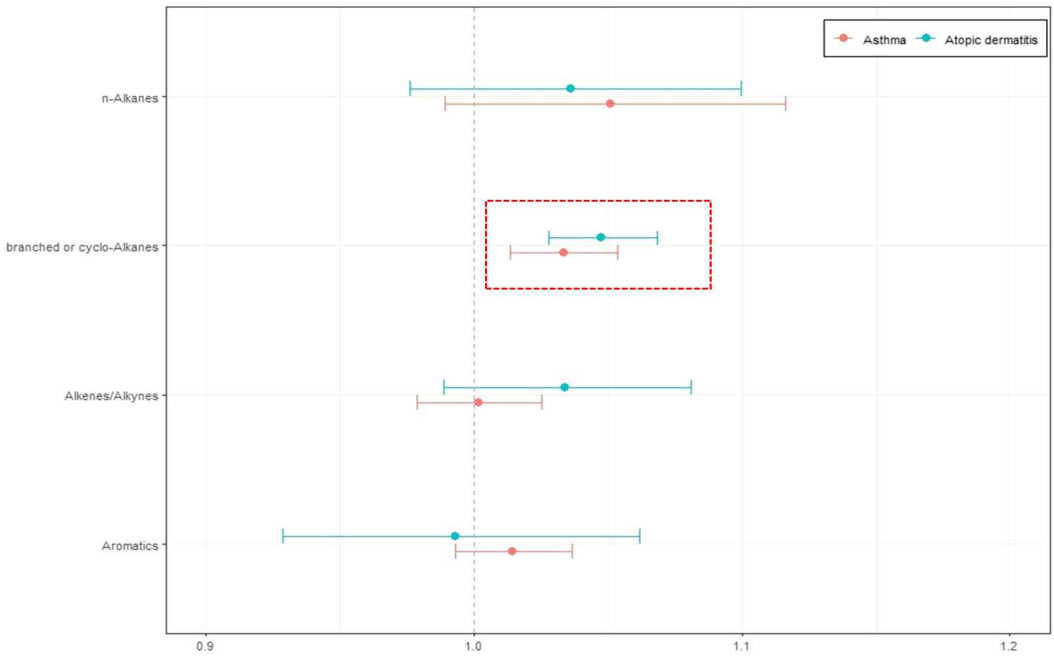
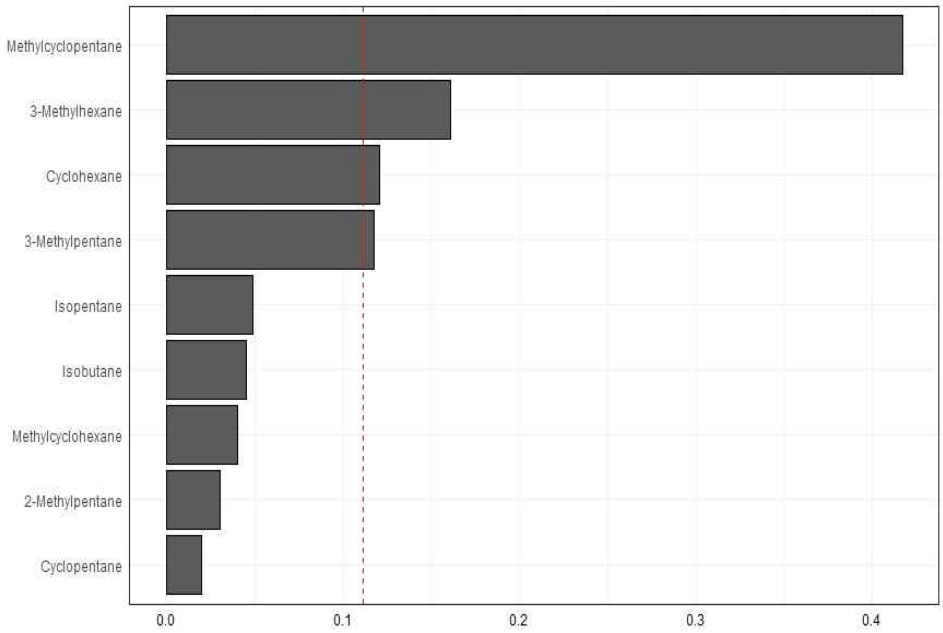


Figure 5. Reltaive risks (95% CI) in medical institution admissions and visits of AD and asthma per quartile increase of the WQS index (at lag 0)

In addition, we identified the key substances that played important roles within branched or cyclo-Alkanes at lag 0 for AD and asthma (Figure 6). For AD, within the branched or cyclo-Alkanes, methlylcyclopentane had the highest weight, followed by 3-methylhexane, cyclohexane, 3-methylpentane (weights: 0.42, 0.16, 0.12, and 0.11, respectively). The most important substance for asthma was methlylcyclopentane was the most important substance, with a weight of 0.52.

(A)



(B)

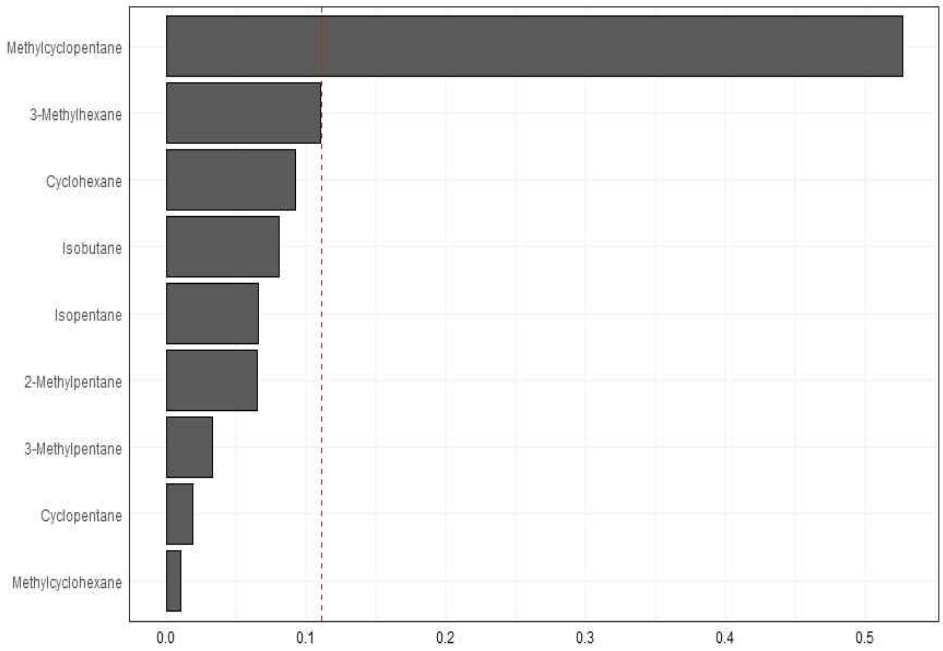


Figure 6. WQS weights for AD and asthma in branched or cyclo-Alkanes (at lag 0)

3-2) Sub-group analysis

The results of the stratified analysis by sex are presented in Table 20. In the sex-stratified analysis, the estimated relative risk for branched or cyclo-Alkanes related to AD was higher in males than in females. Conversely, the estimated relative risk for branched or cyclo-Alkanes related to asthma was higher in females than in males. However, the sex differences in branched or cyclo-Alkanes for both AD and asthma were not statistically significant.

Table 20. Association between exposure to VOC mixtures and medical institution admissions and visits for AD and asthma by sex (at lag 0)

VOCs groups	RR (95% CI) by sex		*p*-value for interaction
	Male	Female	
Atopic dermatitis			
branched or cylco-Alkanes	1.048 (1.025, 1.071)*	1.047 (1.026, 1.067)*	0.949
Asthma			
branched- or cylco- Alkanes	1.030 (1.012, 1.049)*	1.031 (1.015, 1.048)*	0.948

RR: Relative risk, CI: Confidence interval
*p-value <0.05: statistically significant

For the age group-stratified analysis, the associations between exposure to different VOCs and medical institutions stays and visits for AD and asthma are presented in Tables 21. We found that the under-3 and 13-18 age groups exhibited the highest risk associated with branched or cyclo-Alkanes, followed by the 3-6 age group, while the 7-12 age group showed the lowest risk. all of these findings were significant. For asthma, the age group with the highest relative risks for branched or cyclo-Alkanes was 7-12, while no statistically significant association was observed only in the 13-18 age group.

Table 21. Association between exposure to VOC mixtures and medical institution admissions and visits for AD and asthma by age groups (at lag 0)

VOCs groups	RR (95% CI) by age groups				*p*-value for interaction
	<3 yrs	3~6 yrs	7~12 yrs	13~18 yrs	
Atopic dermatitis					
branched or cylco-Alkanes	1.053 (1.033, 1.072)*	1.046 (1.019, 1.074)*	1.033 (1.003, 1.063)*	1.053 (1.029, 1.078)*	0.714
Asthma					
branched or cylco-Alkanes	1.029 (1.009, 1.049)*	1.029 (1.012, 1.045)*	1.036 (1.016, 1.056)*	1.006 (0.983, 1.029)	0.240

RR: Relative risk, CI: Confidence interval
*p-value <0.05: statistically significant

The results of the season-stratified analysis are listed in Table 22. For AD, spring was the season with the highest relative risk associated with branched or cyclo-Alkanes. For asthma, summer had the highest relative risk for branched or cyclo-Alkanes. However, no statistically significant differences were observed between seasons.

Table 22. Association between exposure to VOCs mixture and medical institution admissions and visits for AD and asthma by seasons (at lag 0)

VOCs groups	RR (95% CI) by seasons				*p*-value for interaction
	spring	summer	autumn	winter	
Atopic dermatitis					
branched or cylco-Alkanes	1.065 (1.014, 1.116)*	1.054 (0.995, 1.112)	1.042 (0.980, 1.104)	1.030 (0.986, 1.074)	0.166
Asthma					
branched or cylco-Alkanes	1.038 (1.000, 1.076)	1.053 (1.013, 1.093)*	1.019 (0.974, 1.064)	0.986 (0.940, 1.033)	0.535

RR: Relative risk, CI: Confidence interval
*p-value <0.05: statistically significant

The results of the stratified analysis by sites are listed in Table 23. For AD, site 3 exhibited the highest relative risk associated with branched or cyclo-Alkanes; however, the difference between sites were not statistically significant. For asthma, no statistically significant associations were observed across any of the sites.

Table 23. Association between exposure to VOCs mixture and medical institution admissions and visits for AD and asthma by sites (at lag 0)

VOCs groups	RR (95% CI) by age groups			*p*-value for interaction
	Site 1	Site 2	Site 3	
Atopic dermatitis				
branched or cylco-Alkanes	1.024 (0.962, 1.087)	1.005 (0.956, 1.054)	1.081 (1.018, 1.144)*	0.166
Asthma				
branched or cylco-Alkanes	1.005 (0.969, 1.041)	1.027 (0.994, 1.060)	1.003 (0.972, 1.034)	0.535

RR: Relative risk, CI: Confidence interval
*p-value <0.05: statistically significant

3-3) Sensitivity analysis

The results obtained after adjusting for different air pollutants in the model are presented in Table 24.

For branched or cyclo-Alkanes in AD, all estimated relative risks were lower after adjusting for each air pollutant compared to the main model. The lowest relative risk was observed after adjusting for NO_2, but it was not statically significant. For asthma, the estimated risks were generally lower after adjusting for each air pollutant, with the lowest risk observed after CO adjustment.

Table 24. Relative risk (95% CI) in medical institution visits for AD and asthma per quartile increment of WQS index after adjusting for air pollutants (at lag 0)

VOCs groups	adjust for O_3	adjust for NO_2	adjust for SO_2	adjust for CO	adjust for PM_{10}	adjust for $PM_{2.5}$
Atopic dermatitis						
branched or cylco-Alkanes	1.042 (1.019, 1.065)*	1.028 (1.000, 1.055)	1.041 (1.019, 1.062)*	1.041 (1.016, 1.067)*	1.042 (1.019, 1.064)*	1.042 (1.017, 1.067)*
Asthma						
branched or cylco-Alkanes	1.031 (1.013, 1.048)*	1.031 (1.010, 1.053)*	1.031 (1.011, 1.051)*	1.025 (1.001, 1.049)*	1.030 (1.011, 1.050)*	1.029 (1.007, 1.050)*

*p-value <0.05: statistically significant

4. Association between VOC mixtures and medical institution admissions and visits for AD and asthma using BKMR model

4-1) Overall VOC mixtures effect

We evaluated the effects of exposure to overall VOC mixtures within each group by accounting for non-linear relationships and interactions between substances. The combined effects of overall VOCs in the key VOC group (branched or cyclo-Alkanes) on AD and asthma are illustrated in Figure 7. These figures depict the estimated changes in AD and asthma when exposures are at a specific percentile (x-axis) compared to their corresponding medians. The analysis revealed that combined exposure to branched or cyclo-Alkanes significantly increased the number of medical institutions stays and visits for AD as exposure levels rose from low to high, relative to the the median value. Similarly, for asthma, combined exposure to branched or cyclo-Alkanes significantly increased medical institutions stays and visits as exposure levels increased from low to high, relative to the median value.

To examine the non-linear relationship between each VOC and medical institutions stays and visits for AD and asthma, we investigated the exposure-response functions (Figure S7). For AD, isopentane and methylcyclopentane demonstrated positive relationship in the forward direction, whereas isobutane, 2-methylpentane, and cyclopentane showed an almost linear relationship in the reverse direction. The other substances exhibited a relatively flat curve. In asthma, isopentane, 3-methylhexane, methylcyclopentane, and methylcyclohexane exhibited a nearly linear relationship in the forward direction, whereas isobutane,

2-methylpentane, 3-methylpentane, cyclopentane, and cyclohexane demonstrated a nearly linear relationship in the reverse direction. The other substances presented a relatively flat curve.

Furthermore, this plot illustrates the bivariate interactions between various environmental exposures and their effects on a response variable using BKMR (Figure S8). The interactions are evaluated by plotting the estimated effect of one exposure across different levels of a second exposure, represented by their quantiles (25^{th}, 50^{th}, and 75^{th} percentiles, shown as red, green, and blue lines, respectively). In both AD and asthma, some exposures demonstrate nearly linear interactions in the forward direction. For example, isopentane exhibits a positive linear interaction with methylcyclopentane. This indicates that as the levels of these exposure pairs increase, their combined effect on the response variable consistently increases. Conversely, certain exposures exhibit reverse linear interactions. In such cases, increasing the levels of these exposures results in a decreasing response variable. Additionally, some exposure combinations exhibit minimal interaction effects, as indicated by flat curves in their respective panels. These flat patterns suggest that the combined exposure levels of these variables have little to no impact on the response variable. Overall, the analysis highlights both synergistic and antagonistic interactions among different exposure variables, offering insights into the complex environmental influences on the outcome of interest.

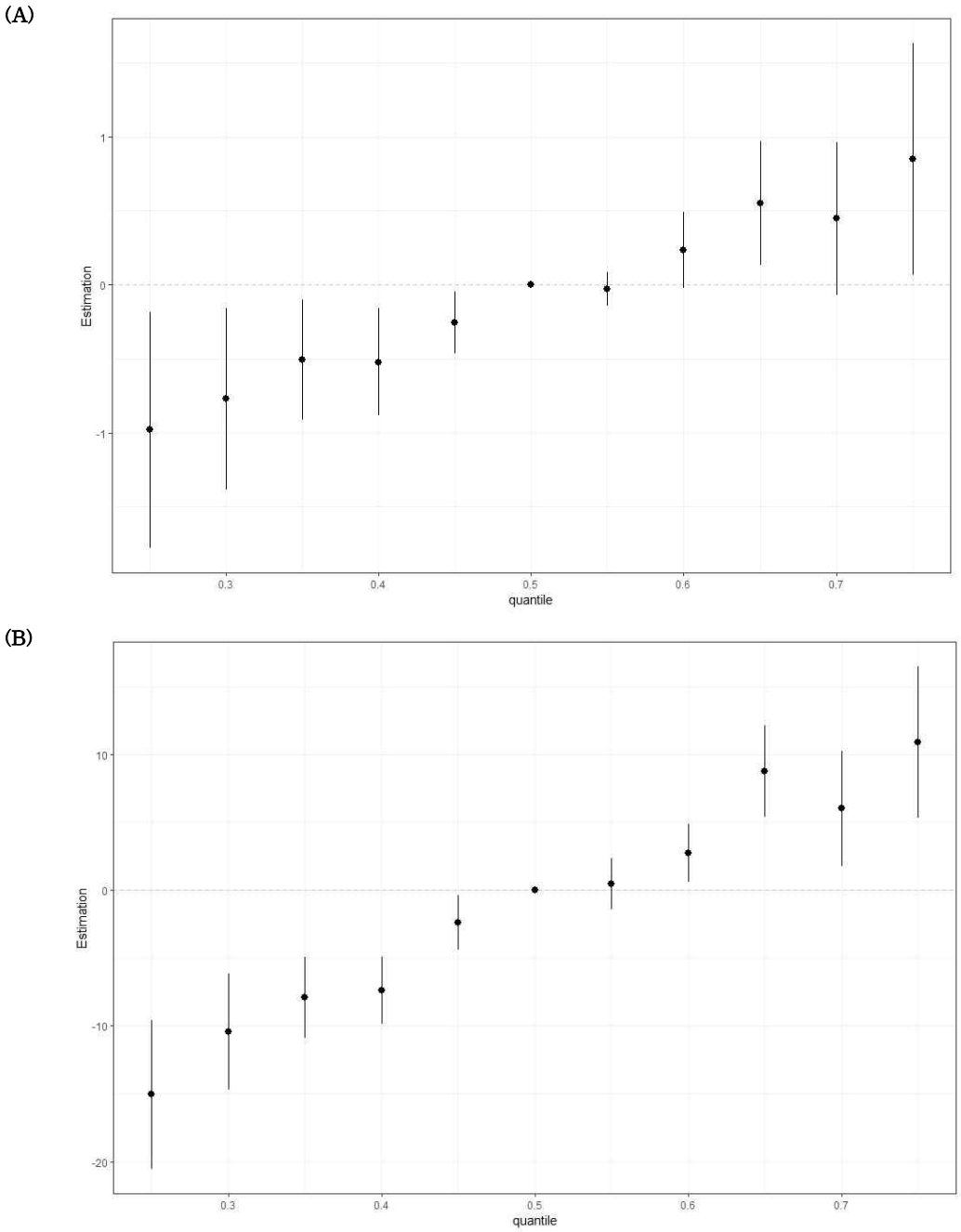


Figure 7. Overall effect of VOC mixtures in branched or cyclo-Alkanes (estimation, 95% CI) on (A) AD and (B) asthma (at lag 0)

5. Attributable number and population attributable fraction of medical institution admissions and visits for AD and asthma due to VOC mixtures

Table 25 presents the attributable number (AN) and population attributable fraction (PAF) of AD- and asthma-related medical institution stays and visits caused by branched or cyclo-Alkanes. The scenarios were based on dividing the total concentrations of the VOC group into quartiles: Scenarios 1, 2, and 3 correspond to the 75th, 50th, and 25th percentiles of sum of branched or cyclo-Alkanes' concentration, respectively.

For AD, the AN attributed to branched or cyclo-Alkanes exposure was 1,342, 3,116, and 5,252 cases under scenarios 1, 2, and 3, respectively, representing 1.8%, 4.3%, and 7.2%. For asthma, the AN attributed to branched or cyclo-Alkanes exposure was 4,932, 11,239, and 18,963 cases under scenarios 1, 2, and 3, respectively, representing 1.2%, 2.8%, and 4.8%.

Table 25. AN and PAF of medical institution admissions and visits for AD and asthma due to VOCs, 2015-2019

VOCs group	Reference concentration (ppb)	AN	PAF(%)
Atopic dermatitis			
branched or cyclo-Alkanes	6.2 (Scenario 1: Q_3)	1,342	1.8
	4.9 (Scenario 2: Q_2)	3,116	4.3
	3.9 (Scenario 3: Q_1)	5,252	7.2
Asthma			
branched or cyclo-Alkanes	6.2 (Scenario 1: Q_3)	4,932	1.2
	4.9 (Scenario 2: Q_2)	11,239	2.8
	3.9 (Scenario 3: Q_1)	18,963	4.8

Q_3: 75th percentile; Q_2: 50th percentile; Q_1: 25th percentile

6. Estimation of costs of AD and asthma attributed to VOC mixtures

Medical expenses, non-medical expenses, and total costs for AD and asthma are presented in Tables 26 and 27.

For AD, the total cost was highest in 2017 (2,979,271 KRW per 1 patient) but has decreased since then. This trend appears to be related to the proportion of inpatient medical costs covered by insurance premiums, which was 82.7% in 2017. In asthma, the highest cost (1,984,110 KRW per 1 patient) was observed in 2018. This was associated with the proportions of inpatient medical costs covered by insurance premiums (67.2%) and transportation costs (14.8%).

Table 26. Total costs of AD (per 1 patient) during 2015-2019

(Unit: KRW)

		2015	2016	2017	2018	2019	Average
Insurance premiums	Outpatient medical cost	56,425 (3.6%)	65,580 (6.4%)	72,784 (2.4%)	80,689 (6.8%)	80,405 (6.5%)	71,177 (4.5%)
	Inpatient medical cost	1,122,449 (72.0%)	629,596 (61.1%)	2,463,748 (82.7%)	776,695 (65.4%)	776,001 (63.2%)	1,153,697 (72.3%)
	Drug prescription cost	27,986 (1.8%)	28,254 (2.7%)	28,844 (1.0%)	29,474 (2.5%)	29,586 (2.4%)	28,829 (1.8%)
Out-of-pocket costs	Outpatient medical cost	30,103 (1.9%)	33,989 (3.3%)	37,232 (1.2%)	41,024 (3.5%)	40,629 (3.3%)	36,595 (2.3%)
	Inpatient medical cost	160,767 (10.3%)	118,086 (11.5%)	208,462 (7.0%)	76,747 (6.5%)	119,180 (9.7%)	136,648 (8.6%)
Non-medial costs	Transport-ation cost for hospital stays and visits	160,767 (10.3%)	154,760 (15.0%)	168,201 (5.6%)	182,165 (15.3%)	181,975 (14.8%)	169,573 (10.6%)
Total costs		1,558,495	1,030,264	2,979,271	1,186,793	1,227,776	1,596,520

Table 27. Total costs of asthma (per 1 patient) during 2015-2019

(Unit: KRW)

		2015	2016	2017	2018	2019	Average
Insurance premiums	Outpatient medical cost	109,005 (5.7%)	126,180 (6.5%)	130,389 (6.7%)	147,899 (7.5%)	141,902 (8.5%)	131,075 (7.0%)
	Inpatient medical cost	1,272,866 (66.9%)	1,276,464 (65.7%)	1,288,652 (66.5%)	1,333,794 (67.2%)	1,035,067 (62.2%)	1,241,369 (65.8%)
	Drug prescription cost	20,554 (1.1%)	20,801 (1.1%)	20,735 (1.1%)	20,840 (1.1%)	19,772 (1.2%)	20,541 (1.1%)
Out-of-pocket costs	Outpatient medical cost	35,112 (1.8%)	38,008 (2.0%)	38,161 (2.0%)	38,324 (1.9%)	40,093 (2.4%)	37,939 (2.0%)
	Inpatient medical cost	203.229 (10.7%)	210,447 (10.8%)	177,943 (9.2%)	149,050 (7.5%)	150,233 (9.0%)	178,181 (9.4%)
Non-medial costs	Transport-ation cost for hospital stays and visits	261,309 (13.7%)	269,981 (13.9%)	281,444 (14.5%)	294,203 (14.8%)	276,925 (16.6%)	276,772 (14.7%)
Total costs		1,902,075	1,941,880	1,937,323	1,984,110	1,663,993	1,885,876

For AD, the total expenses, including insurance premiums and out-of-pocket expenses, attributed to branched or cyclo-Alkanes were highest in 2017 across all three scenarios, reflecting the overall trend of total AD-related costs. For asthma, the highest total expenses across all three scenarios were recorded in 2018, consistent with the trend observed in asthma-related total costs.

Table 28. Attributable total costs (overall and per 1 person) for AD due to VOC mixtures during 2015-2019

(Unit: 10,000 KRW)

VOC group	Year	scenario1		scenario2		scenario3	
		overall ACtotal	AC_{total} (per 1 person)	overall ACtotal	AC_{total} (per 1 person)	overall ACtotal	AC_{total} (per 1 person)
branched or cyclo-Alkanes	2015	216,609	3.0	504,285	6.9	871,430	11.9
	2016	143,192	2.0	333,364	4.6	576,070	7.9
	2017	414,078	5.7	964,008	13.2	1,665,855	22.7
	2018	164,948	2.3	384,013	5.2	663,593	9.1
	2019	170,644	2.3	397,274	5.4	686,509	9.4
	Average	**221,894**	**3.0**	**516,589**	**7.1**	**892,692**	**12.2**

Table 29. Attributable total costs (overall and per 1 person) for asthma due to VOC mixture during 2015-2019

(Unit: 10,000 KRW)

VOC group	Year	scenario1		scenario2		scenario3	
		overall ACtotal	AC_{total} (per 1 person)	overall ACtotal	AC_{total} (per 1 person)	overall ACtotal	AC_{total} (per 1 person)
branched or cyclo-Alkanes	2015	1,050,052	2.6	2,378,280	6.0	4,005,764	10.1
	2016	1,072,026	2.7	2,428,050	6.1	4,089,593	10.3
	2017	1,069,510	2.7	2,422,352	6.1	4,079,996	10.3
	2018	1,095,339	2.8	2,480,853	6.3	4,178,529	10.5
	2019	918,617	2.3	2,080,590	5.3	3,504,363	8.8
	Average	**1,041,109**	**2.6**	**2,358,025**	**6.0**	**3,971,649**	**10.0**

V. DISCUSSION

Our study is the first to introduce a method for identifying critical components of ambient VOC mixtures based on their impact on public health. This method examines the acute effects of these mixtures on medical institution admissions and visits related to atopic dermatitis (AD) and asthma. The findings validate the applicability of this approach, demonstrating significant associations between branched or cyclo-Alkanes and both AD and asthma. Previous epidemiological evidence has shown an association between hydrocarbon groups, particularly iso/anteiso-alkane and/or cycloalkane groups, and emergency department visits for both asthma as well as cardiovascular diseases [35, 48].

Our study evaluated the combined effects of ambient VOC mixtures and found that these mixtures can increase the risk of AD and asthma, thereby addressing a gap in epidemiological evidence regarding the effects of low concentrations of ambient VOCs. However, there are few epidemiological studies investigating the association between short-term exposure to ambient VOC mixtures and AD and asthma.

Based on the results of WQSR and BKMR, methylcyclopentane has been consistently identified as the key substance influencing AD and asthma within the branched and cyclo-Alkanes group. Skin irritation and aspiration toxicities, as outlined in the EU CLP toxicity classification (Table S3), indicate that lipophilic VOCs can be absorbed through the skin, nasal mucosa, the respiratory tract epithelium, and cellular membranes of various organs, subsequently inducing adverse outcomes [8]. Nevertheless, the human health effects of methylcyclopentane have rarely been discussed in the literature.

In addtion, the primary emission sources of these VOCs are likely related to traffic, specifically gasoline and LPG emissions.

This study presents several strengths. First, we examined 30 VOCs, which exceeds the number of VOCs analyzed in previous studies, and medical institutions admission and visits data for AD and asthma covered all secondary and tertiary hospitals in Seoul. Second, the VOCs were grouped based on their phyicochemical characteristics, facilitating a more detailed analysis of their sources and atmospheric processes. Lastly, the WQSR and BKMR models were employed to assess the association between short-term exposure to the VOC exposome and medical institution admissions and visits related to AD and asthma, enabling the exploration of combined effects and the identification of key components. To validate the findings from the WQSR and BKMR models, Generalized Additive Model (GAM) was utilized to establish the exposure-response relationship, thereby enhancing the stability and credibility of the results.

This study has several limitations. First, the challenge of monitoring individual exposure levels led to the use of VOC concentrations from environmental monitoring sites to represent population-level exposure, which may result in exposure misclassification. Additionally, the lack of individual-level temporal activity data represents another potential source of misclassification, a common limitation in many time series studies investigating the relationship between air pollution and health. Furthermore, this research was conducted in a single city, Seoul, with a limited number of VOC monitoring stations, which restricts the generalizability of the findings. Therefore, further multicenter studies are warranted to incorporate a larger number of monitoring stations, thereby enhancing data collection for subsequent analyses. Finally, the VOC chemicals in this study focused on

photochemical air pollutants known to generate ozone. This study exclusively analyzed normal hydrocarbons, excluding VOCs with diverse functional groups. Further research including heterogeneous hydrocarbons isl expected to facilitate a more comprehensive investigation of the relationship between VOC mixtures, chemical toxicity, and health effects.

Using the integrated methodology employed in this study, we assessed the combined effects of ambient VOCs on medical institution admissions and visits for AD and asthma, identifying key substances that significantly contribute to these outcomes. Our findings indicate that even at extremely low concentrations, ambient VOCs can still lead to development or exacerbation of AD and asthma.

Ⅵ. CONCLUSION

The study examined the relationship between individual VOCs and VOC mixtures, as well as medical institutions admissions and visits for AD and asthma among individuals under 19 years of age in Seoul. We found that the branched or cyclo-Alkanes group was associated with both AD and asthma, possibly due to toxicity related to their chemical structure. Additionally, we estimated the burden of these diseases attributed to VOC mixtures in terms of Population Attributable Fractions (PAFs) and the economic costs incurred by medical institution admissions and visits. To the best of our knowledge, this is the first domestic study to estimate the burden of these diseases attributed to VOC mixtures. Our findings could provide a scientific basis for more targeted efforts to control VOC emissions with high health risks, particularly for vulnerable groups such as children.

SUPPLEMENTARY MATERIALS

Table S1. Trends of yearly medical institution admissions or visits for AD in Seoul, 2015-2019

	2015	2016	2017	2018	2019
Total	15,099	14,875	15,347	14,292	13,643
Age group					
0~2 yrs old	4,447	4,238	4,263	3,003	2,063
3~6 yrs old	4,324	4,170	4,215	4,365	4,804
7~12 yrs old	4,012	4,130	4,153	4,077	3,870
13~18 yrs old	2,316	2,337	2,716	2,847	2,906
Sex					
Male	8,501	8,678	8,885	7,973	7,589
Female	6,598	6,197	6,462	6,319	6,054

Table S2. Trends of yearly medical institution admissions or visits for asthma in Seoul, 2015-2019

	2015	2016	2017	2018	2019
Total	76,301	90,045	80,889	79,809	69,246
Age group					
0~2 yrs old	22,741	30,128	29,642	26,884	15,331
3~6 yrs old	33,210	35,475	31,156	33,712	33,776
7~12 yrs old	16,105	18,909	15,213	14,412	14,766
13~18 yrs old	4,245	5,533	4,878	4,801	5,373
Sex					
Male	44,589	51,830	46,248	45,433	40,136
Female	31,712	38,215	34,641	34,376	29,110

Table S3. Physico-chemical properties and toxicity classification of 30 VOCs

Group	Substance	CASRN	MW*	log K_{ow}*	Toxicity Classification*
n-Alkanes	Ethane	74-84-0	30.1	1.8	-
	Propane	74-98-6	44.1	2.2	-
	n-Butane	106-97-8	58.1	2.7	Muta. 1B, Carc. 1A
	n-Pentane	109-66-0	72.2	3.3	Asp. Tox. 1, STOT SE 3
	Hexane	110-54-3	86.2	3.8	Skin Irrit. 2 Asp. Tox. 1 STOT SE 3 STOT RE 2 Repr. 2
	n-Heptane	142-82-5	100.2	4.3	Skin Irrit. 2 Asp. Tox. 1 STOT SE 3
	n-Octane	111-65-9	114.2	4.8	Skin Irrit. 2 Asp. Tox. 1 STOT SE 3
	n-Nonane	111-84-2	128.2	5.3	Skin Irrit. 2 Asp. Tox. 1 STOT SE 3
	n-Decane	124-18-5	142.3	5.8	Asp. Tox. 1
	n-Undecane	1120-21-4	156.3	6.3	Asp. Tox. 1
	n-Dodecane	112-40-3	170.3	6.8	Asp. Tox. 1
branched or cyclo-Alkanes	Isobutane	75-28-5	58.1	2.8	Muta. 1B Carc. 1A
	Isopentane	78-78-4	72.2	2.7	Asp. Tox. 1 STOT SE 3
	2-Methylpentane	107-83-5	86.2	3.6	Skin Irrit. 2 Asp. Tox. 1 STOT SE 3
	3-Methylpentane	96-14-0	86.2	3.6	Skin Irrit. 2 Asp. Tox. 1 STOT SE 3
	3-Methylhexane	589-34-4	100.2	4.1	Skin Irrit. 2 Asp. Tox. 1 STOT SE 3
	Cyclopentane	287-92-3	70.1	3.0	-
	Cyclohexane	110-82-7	84.2	3.4	Skin Irrit. 2 Asp. Tox. 1 STOT SE 3
	Methylcyclopentane	96-37-7	84.2	3.4	Skin Irrit. 2 Asp. Tox. 1 STOT SE 3
	Methylcyclohexane	108-87-2	98.2	3.6	Skin Irrit. 2 Asp. Tox. 1 STOT SE 3

Group	Substance	CASRN	MW*	log K_{ow}*	Toxicity Classification*
Alkenes/ Alkynes	Acetylene	74-86-2	26.0	0.4	-
	Ethylene	74-85-1	28.1	1.1	STOT SE 3
	Propylene	115-07-1	42.1	1.8	-
	1-Butene	106-98-9	56.1	2.3	-
Aromatics	Benzene	71-43-2	78.1	2.1	Skin Irrit. 2 Eye Irrit. 2 Asp. Tox. 1 Muta. 1B Carc. 1A
	Ethylbenzene	100-41-4	106.2	3.3	Acute Tox. 4 Asp. Tox. 1 STOT RE 2
	Toluene	108-88-3	92.1	2.7	Skin Irrit. 2 Asp. Tox. 1 STOT SE 3 STOT RE 2 Repr. 2
	m/p-Xylene	108-38-3; 106-42-3	106.2	3.2	Skin Irrit. 2 Acute Tox. 4
	o-Xylene	95-47-6	106.2	3.1	Skin Irrit. 2 Acute Tox. 4
	1,2,4-Trimethylbenzene	95-63-6	120.2	3.8	Skin Irrit. 2 Eye Irrit. 2 Acute Tox. 4 STOT SE 3

*MW: Molecular weight; log K_{ow}: Octanol-water partition coefficient, which measures of chemical's hydrophobicity
*The toxicity classification followed the EU CLP classification; Acute Tox: Acute toxicity, Eye Irrit: Eye irritation, Skin Irrit: Skin irritation, Asp. Tox: Aspriation toxicitiy, STOT SE: Specific target organ toxicity-single exposure, STOT RE: Specific target organ toxicity-repeated exposure, Repr: Reproductive toxcity, Muta: Mutagenic toxicity, Carc: Carcinogenic toxicity

Table S4. Annual average concentrations of air pollutants in Seoul, 2015-2019

	VOCs (ppb)	O_3 (ppb)	NO_2 (ppb)	SO_2 (ppb)	CO (ppb)	PM_{10} ($\mu g/m^3$)	$PM_{2.5}$ ($\mu g/m^3$)
2015	33.0	22.4	32.0	5.4	519.4	45.2	23.1
2016	27.0	23.9	31.4	4.9	524.7	47.8	26.2
2017	26.0	24.8	29.6	4.6	519.6	43.8	24.7
2018	43.8	23.3	28.2	4.4	504.2	39.7	22.8
2019	34.0	24.9	28.1	3.9	525.3	41.4	24.7

Table S5. Descriptive statistics of VOC groups and substances

VOC Substance	%>LOQ	Mean ± SD	Min	Q_1	Median	Q_3	IQR
***n*-Alkanes (ppb)**		17.5 ± 7.3	4.0	12.1	16.4	21.7	9.6
Ethane	98.2	6.0 ± 2.8	0.8	3.8	5.5	7.8	4.0
Propane	98.6	5.0 ± 2.4	1.0	3.2	4.6	6.3	3.1
n-Butane	99.2	3.9 ± 2.1	0.4	2.3	3.3	5.2	2.9
n-Pentane	95.9	0.9 ± 0.4	0.2	0.6	0.8	1.1	0.5
Hexane	96.5	0.8 ± 0.4	0.1	0.4	0.7	1.0	0.6
n-Heptane	87.2	0.2 ± 0.1	0.07	0.1	0.2	0.3	0.1
n-Octane	74.5	0.2 ± 0.08	0.06	0.1	0.2	0.2	0.08
n-Nonane	87.7	0.2 ± 0.08	0.06	0.1	0.1	0.2	0.07
n-Decane	91.3	0.2 ± 0.1	0.05	0.1	0.2	0.2	0.1
n-Undecane	78.2	0.1 ± 0.07	0.05	0.08	0.09	0.1	0.06
n-Dodecane	73.8	0.1 ± 0.05	0.04	0.07	0.08	0.1	0.04
branched or cyclo-Alkanes (ppb)		5.2 ± 1.8	1.6	3.9	4.9	6.2	2.4
Isobutane	98.2	2.0 ± 0.9	0.4	1.3	1.8	2.5	1.2
Isopentane	96.5	1.4 ± 0.6	0.1	0.9	1.3	1.7	0.7
2-Methylpentane	79.0	0.3 ± 0.2	0.08	0.2	0.3	0.4	0.2
3-Methylpentane	71.6	0.3 ± 0.1	0.08	0.2	0.2	0.3	0.1
3-Methylhexane	72.9	0.2 ± 0.07	0.07	0.1	0.1	0.2	0.07
Cyclopentane	80.4	0.3 ± 0.3	0.1	0.2	0.2	0.4	0.2
Cyclohexane	72.1	0.2 ± 0.09	0.08	0.1	0.2	0.3	0.1
Methylcyclopentane	86.5	0.3 ± 0.2	0.08	0.2	0.3	0.4	0.2
Methylcyclohexane	81.5	0.2 ± 0.08	0.07	0.1	0.2	0.2	0.1
Alkenes/Alkynes (ppb)		4.0 ± 1.6	1.3	2.7	3.7	4.9	2.2
Acetylene	75.1	0.9 ± 0.5	0.3	0.6	0.8	1.2	0.6
Ethylene	97.9	2.1 ± 1.0	0.4	1.3	1.8	2.7	1.3
Propylene	89.6	0.7 ± 0.3	0.2	0.4	0.7	0.9	0.4
1-Butene	71.5	0.3 ± 0.1	0.1	0.2	0.3	0.3	0.1
Aromatics (ppb)		7.4 ± 3.2	1.5	5.1	6.9	9.1	4.1
Benzene	93.2	0.5 ± 0.2	0.1	0.3	0.4	0.6	0.3
Ethylbenzene	98.2	0.9 ± 0.5	0.1	0.5	0.8	1.1	0.5
Toluene	98.5	4.2 ± 2.0	0.5	2.7	4.0	5.4	2.7
m/p-Xylene	99.5	1.1 ± 0.6	0.1	0.7	1.0	1.4	0.7
o-Xylene	97.6	0.5 ± 0.3	0.08	0.3	0.4	0.6	0.3
1,2,4-Trimethylbenzene	84.9	0.2 ± 0.1	0.06	0.1	0.2	0.2	0.1

LOQ: Limit of quantification, SD: Standard deviation, Q_1: 25 percentiles, Q_3: 75 percentiles, IQR: Inter-quartile range

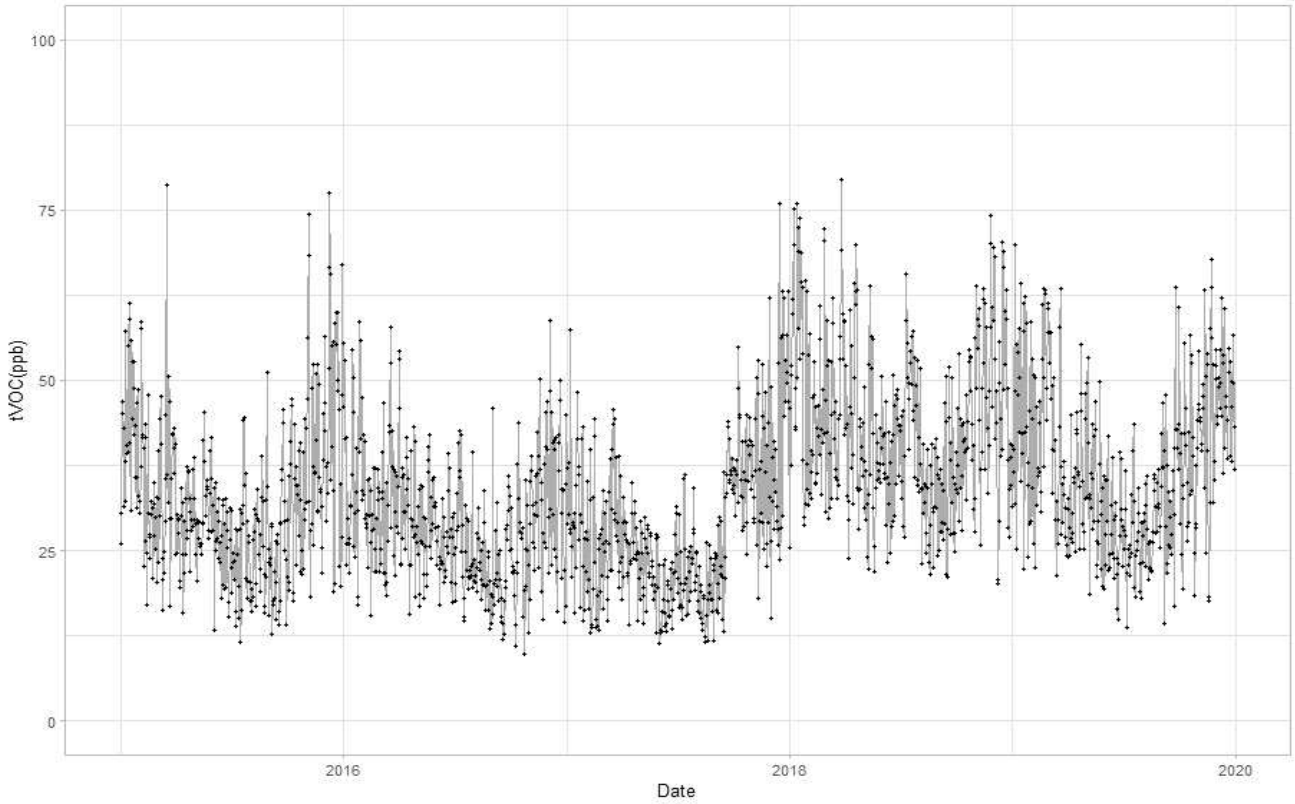


Figure S1. Time-series data of tVOC (2015~2019)

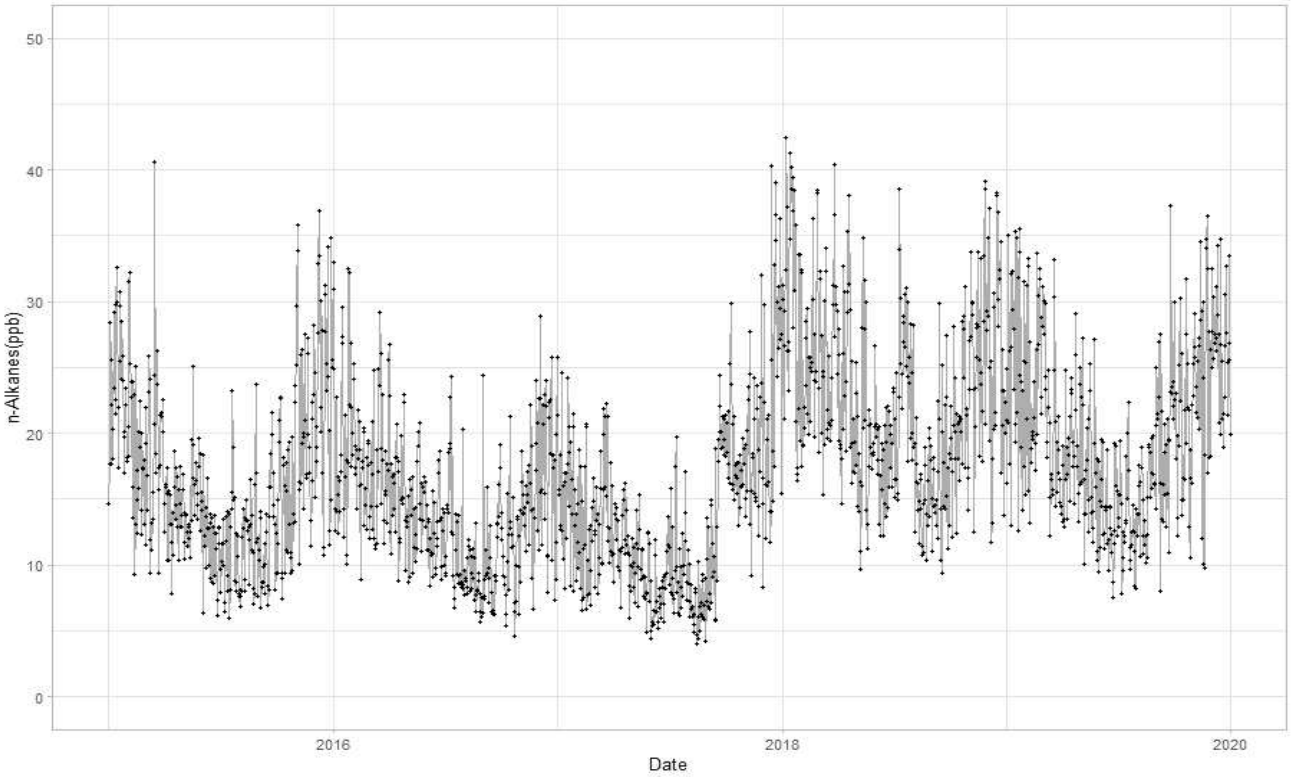


Figure S2. Time-series data of *n*-Alkanes (2015~2019)

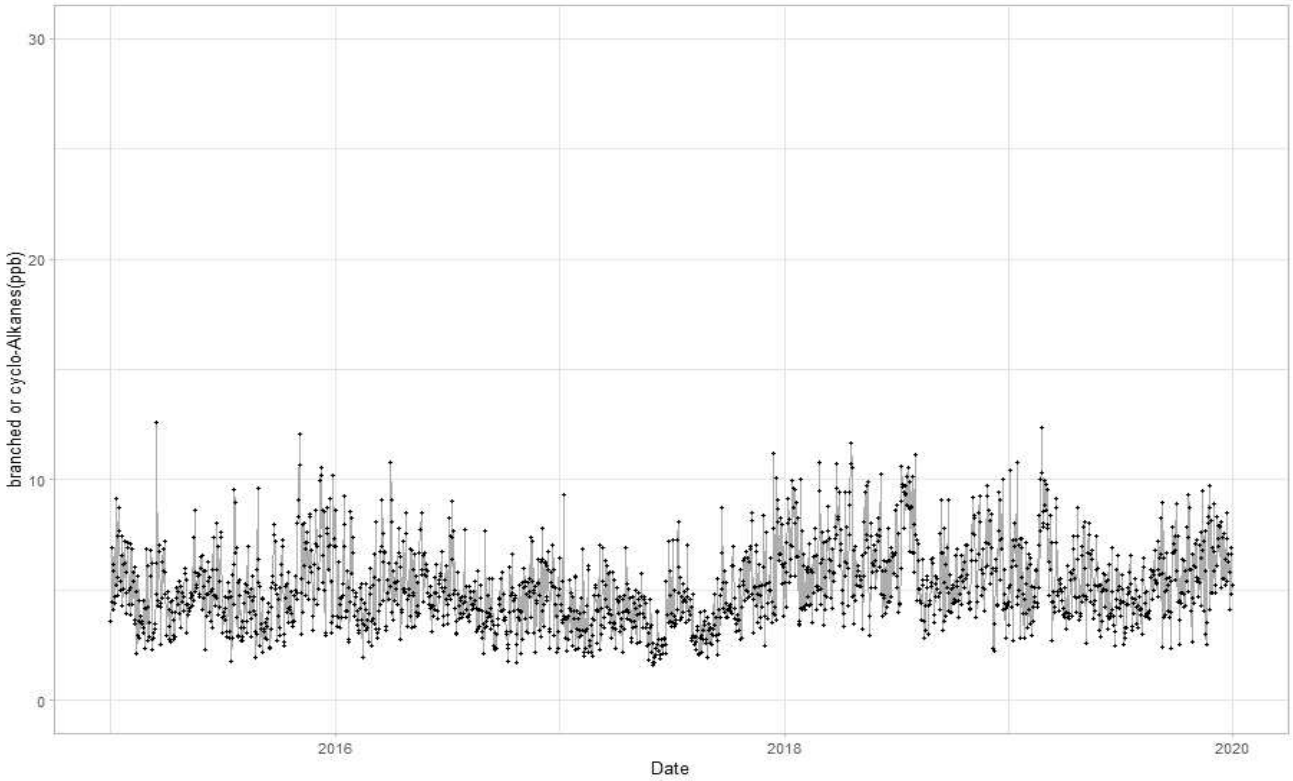


Figure S3. Time-series data of branched or cyclo-Alkanes (2015~2019)

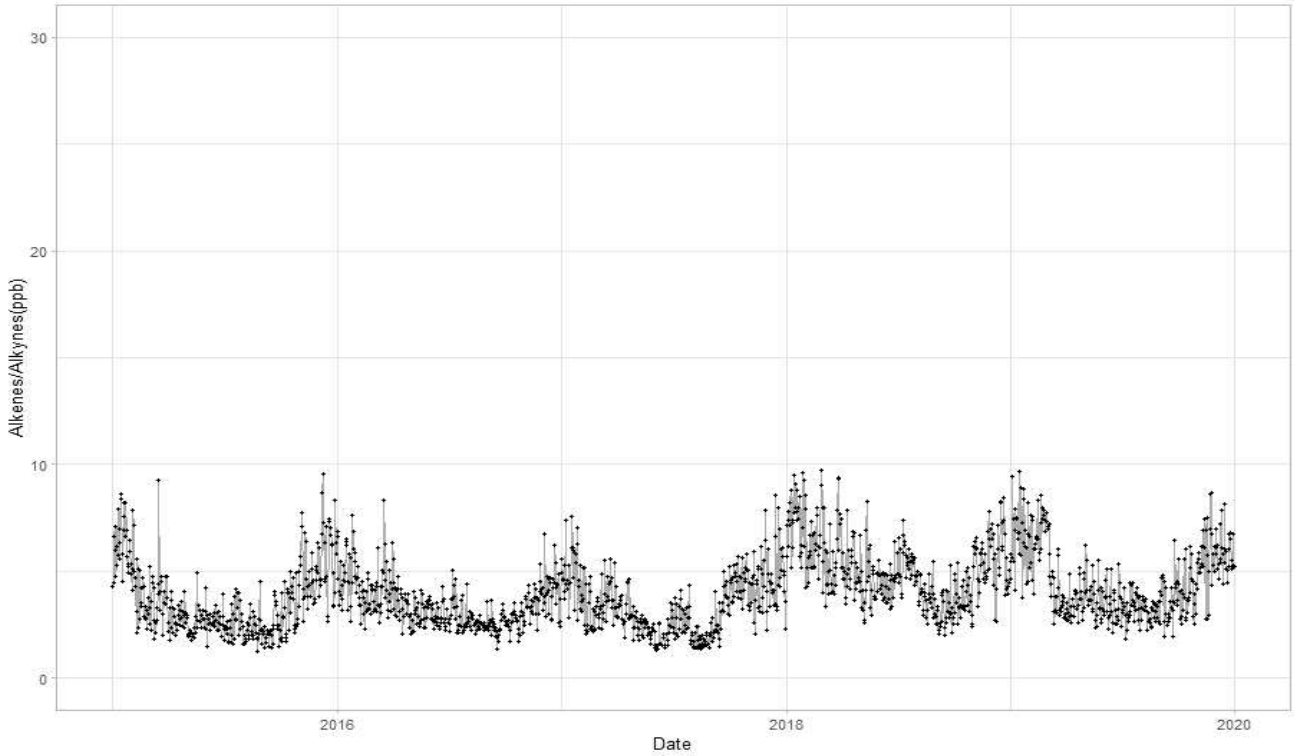


Figure S4. Time-series data of Alkenes/Alkynes (2015~2019)

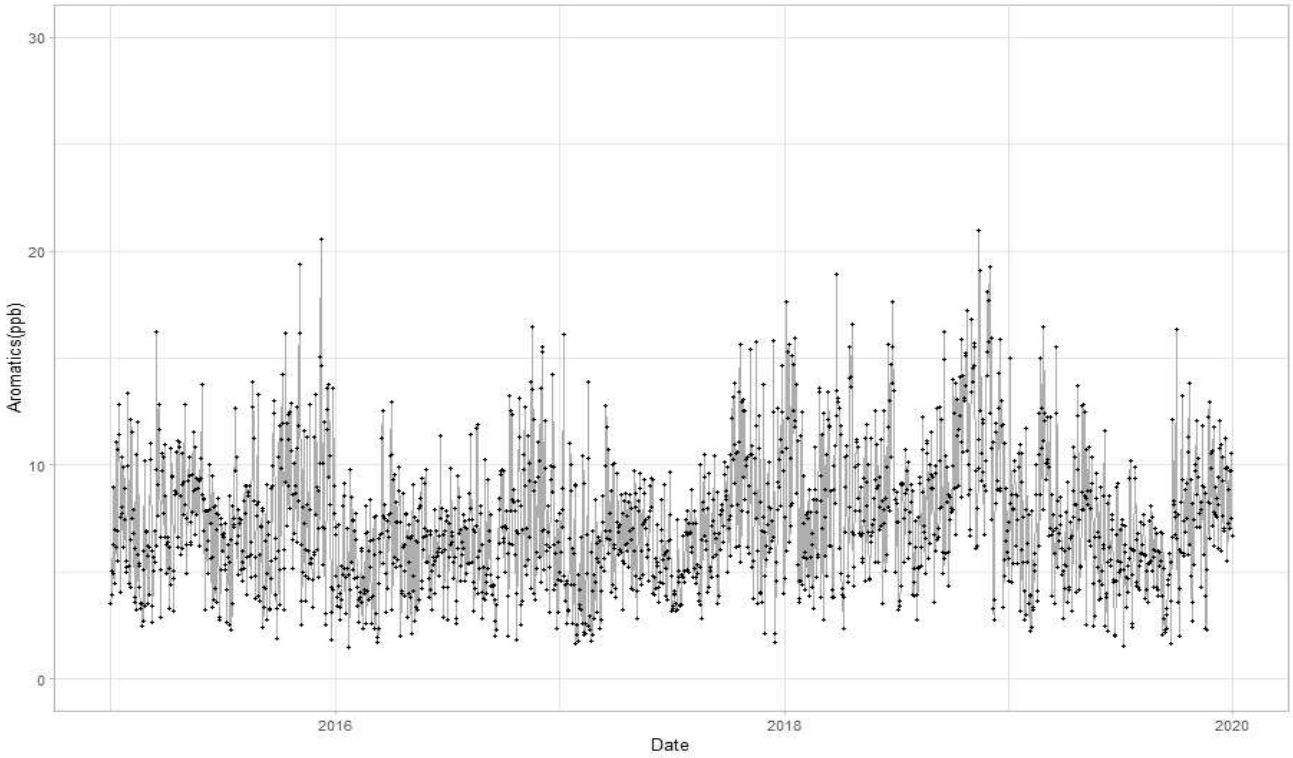


Figure S5. Time-series data of Aromatics (2015~2019)

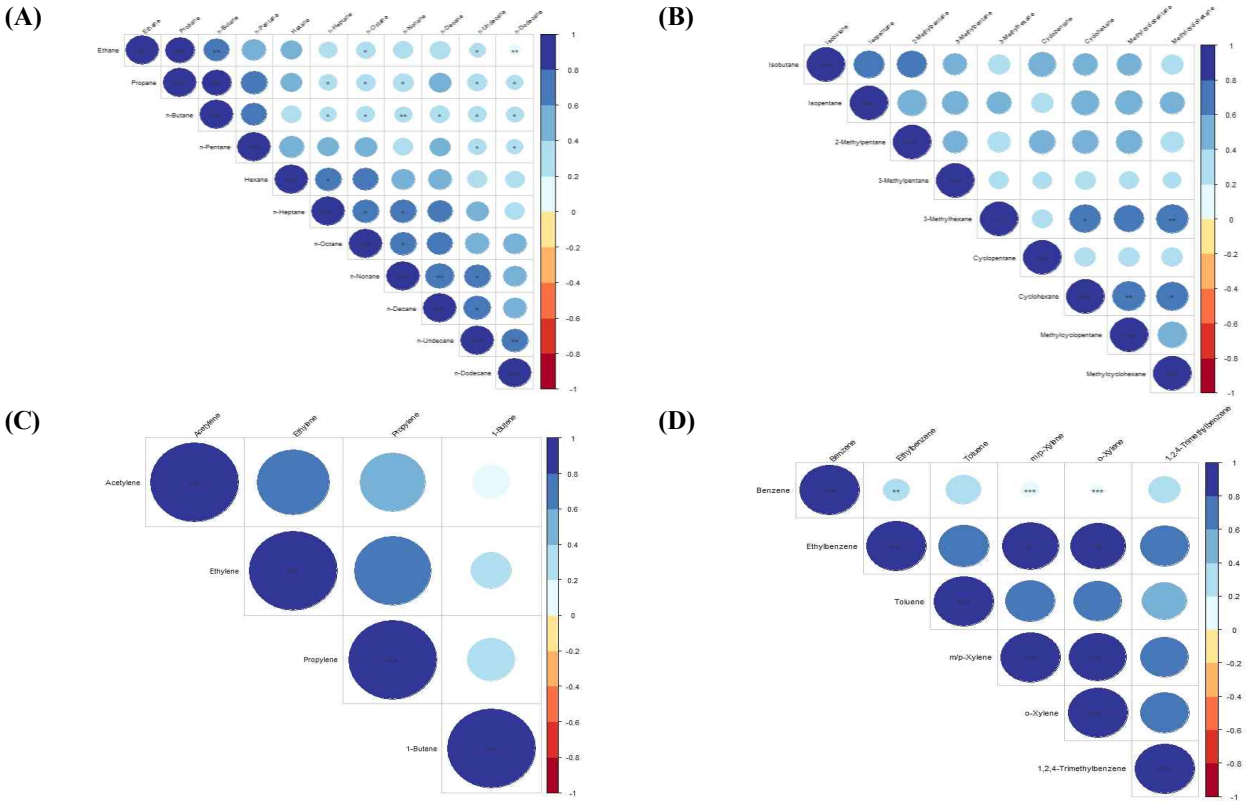


Figure S6. Correlation plot of each VOC groups; (A) *n*-Alkanes, (B) branched or cylco-Alkanes, (C) Alkenes/Alkynes, (D) Aromatics (***: *p*-value <0.001, **: *p*-value <0.01, *: *p*-value <0.05)

Table S6. Relative Risk (95% CI) in hospital admissions and visits for AD per IQR increase of VOC compounds by different single-day lags

Substance	lag0	lag1	lag2	lag3	lag4
***n*-Alkanes**					
Ethane	1.032 (0.985, 1.082)	0.981 (0.932, 1.032)	0.988 (0.941, 1.037)	0.983 (0.936, 1.032)	0.982 (0.938, 1.029)
Propane	1.059 (1.019, 1.101)*	0.958 (0.918, 0.999)	1.017 (0.976, 1.059)	0.966 (0.928, 1.006)	1.014 (0.976, 1.054)
n-Butane	1.050 (1.008, 1.094)*	0.960 (0.919, 1.004)	1.012 (0.969, 1.057)	0.956 (0.915, 1.000)	1.030 (0.988, 1.074)
n-Pentane	1.021 (0.989, 1.055)	0.959 (0.926, 0.993)	1.015 (0.982, 1.050)	0.992 (0.959, 1.026)	1.023 (0.992, 1.056)
Hexane	1.026 (0.989, 1.064)	0.902 (0.868, 0.938)	0.980 (0.943, 1.017)	0.998 (0.962, 1.035)	1.080 (1.043, 1.118)*
n-Heptane	1.028 (1.006, 1.051)*	0.967 (0.945, 0.990)	0.984 (0.962, 1.007)	0.996 (0.974, 1.018)	1.026 (1.004, 1.049)*
n-Octane	1.026 (1.005, 1.049)*	0.969 (0.946, 0.991)	0.985 (0.963, 1.008)	0.999 (0.978, 1.021)	1.019 (0.997, 1.041)
n-Nonane	1.036 (1.017, 1.056)*	0.980 (0.960, 1.001)	0.986 (0.966, 1.006)	1.000 (0.981, 1.020)	0.995 (0.976, 1.015)
n-Decane	1.037 (1.017, 1.058)*	0.967 (0.946, 0.988)	0.992 (0.972, 1.013)	0.988 (0.969, 1.008)	1.015 (0.995, 1.036)
n-Undecane	1.023 (1.004, 1.042)*	0.979 (0.959, 1.000)	0.989 (0.969, 1.009)	0.991 (0.971, 1.011)	1.003 (0.983, 1.023)
n-Dodecane	1.017 (0.997, 1.037)	0.986 (0.965, 1.007)	1.002 (0.981, 1.023)	0.986 (0.965, 1.007)	1.022 (1.001, 1.043)*
branched and cyclo-Alkanes					
Isobutane	1.036 (0.999, 1.075)	0.981 (0.943, 1.020)	1.004 (0.966, 1.043)	0.977 (0.94, 1.015)	1.010 (0.975, 1.047)
Isopentane	1.042 (1.012, 1.073)*	0.972 (0.942, 1.003)	1.021 (0.990, 1.053)	0.984 (0.955, 1.015)	1.012 (0.984, 1.042)
2-Methylpentane	1.028 (1.001, 1.055)*	0.961 (0.934, 0.989)	0.988 (0.960, 1.016)	0.98 (0.953, 1.008)	1.025 (0.998, 1.052)
3-Methylpentane	1.014 (0.997, 1.031)	0.985 (0.967, 1.002)	0.993 (0.976, 1.011)	0.987 (0.97, 1.005)	1.010 (0.993, 1.027)
3-Methylhexane	1.036 (1.014, 1.058)*	0.949 (0.928, 0.972)	0.993 (0.972, 1.015)	0.997 (0.975, 1.018)	1.030 (1.008, 1.052)*
Cyclopentane	1.003 (0.984, 1.022)	0.976 (0.957, 0.996)	1.008 (0.989, 1.029)	0.988 (0.968, 1.008)	1.015 (0.996, 1.035)
Cyclohexane	1.036 (1.010, 1.063)*	0.947 (0.921, 0.973)	0.973 (0.948, 0.999)	0.993 (0.968, 1.019)	1.059 (1.032, 1.086)*
Methylcyclopentane	1.077 (1.045, 1.110)*	0.929 (0.899, 0.959)	0.984 (0.955, 1.015)	0.977 (0.947, 1.007)	1.052 (1.021, 1.083)*
Methylcyclohexane	1.032 (1.005, 1.060)*	0.952 (0.925, 0.979)	0.981 (0.955, 1.008)	0.993 (0.967, 1.020)	1.046 (1.018, 1.074)*

Substance	lag0	lag1	lag2	lag3	lag4
Alkenes/Alkynes					
Acetylene	1.047 (1.006, 1.090)*	0.960 (0.919, 1.003)	0.991 (0.949, 1.035)	0.939 (0.899, 0.982)	1.042 (1.000, 1.085)
Ethylene	1.049 (1.006, 1.094)*	0.959 (0.917, 1.004)	0.972 (0.929, 1.016)	0.986 (0.944, 1.030)	1.007 (0.967, 1.050)
Propylene	1.044 (1.005, 1.084)*	0.990 (0.952, 1.030)	0.964 (0.927, 1.003)	1.006 (0.968, 1.045)	0.986 (0.949, 1.024)
1-Butene	1.006 (0.980, 1.033)	0.975 (0.948, 1.002)	0.986 (0.959, 1.012)	0.996 (0.969, 1.022)	1.009 (0.983, 1.035)
Aromatics					
Benzene	1.059 (1.012, 1.108)*	0.945 (0.901, 0.993)	0.991 (0.945, 1.040)	0.970 (0.925, 1.017)	1.044 (0.999, 1.091)
Ethylbenzene	1.041 (1.014, 1.069)*	0.953 (0.927, 0.981)	0.994 (0.968, 1.021)	0.997 (0.971, 1.024)	1.024 (0.999, 1.051)
Toluene	1.041 (1.008, 1.074)*	0.875 (0.846, 0.905)	0.980 (0.949, 1.012)	0.995 (0.964, 1.027)	1.090 (1.057, 1.123)*
m/p-Xylene	1.029 (1.000, 1.059)	0.952 (0.924, 0.982)	0.994 (0.966, 1.023)	0.998 (0.970, 1.027)	1.025 (0.997, 1.054)
o-Xylene	1.030 (1.001, 1.060)*	0.958 (0.929, 0.987)	0.988 (0.960, 1.017)	0.999 (0.971, 1.028)	1.021 (0.992, 1.050)
1,2,4-Trimethylbenzene	1.036 (1.014, 1.058)*	0.967 (0.945, 0.990)	0.983 (0.961, 1.005)	0.990 (0.969, 1.011)	1.021 (1.000, 1.043)

*p-value <0.05: statistically significant

Table S7. Relative Risk (95% CI) in hospital admissions and visits for AD per IQR increase of VOC compounds by different moving-average lags

Substance	lag01	lag02	lag03	lag04
***n*-Alkanes**				
Ethane	1.013 (0.958, 1.072)	1.003 (0.940, 1.071)	0.999 (0.930, 1.074)	0.992 (0.918, 1.073)
Propane	1.022 (0.975, 1.071)	1.025 (0.971, 1.082)	1.016 (0.958, 1.078)	1.024 (0.960, 1.093)
n-Butane	1.012 (0.965, 1.061)	1.013 (0.960, 1.068)	1.003 (0.947, 1.064)	1.016 (0.954, 1.082)
n-Pentane	0.989 (0.951, 1.027)	0.996 (0.952, 1.041)	1.007 (0.959, 1.058)	1.023 (0.970, 1.080)
Hexane	0.932 (0.893, 0.972)	0.915 (0.871, 0.961)	0.937 (0.887, 0.989)	0.984 (0.928, 1.044)
n-Heptane	0.996 (0.969, 1.024)	0.984 (0.953, 1.017)	0.989 (0.954, 1.026)	1.007 (0.969, 1.047)
n-Octane	0.997 (0.970, 1.026)	0.985 (0.952, 1.019)	0.991 (0.954, 1.029)	1.007 (0.966, 1.049)
n-Nonane	1.016 (0.990, 1.042)	1.005 (0.976, 1.035)	1.008 (0.975, 1.041)	1.005 (0.971, 1.042)
n-Decane	1.005 (0.980, 1.031)	0.999 (0.970, 1.029)	0.996 (0.965, 1.029)	1.005 (0.970, 1.040)
n-Undecane	1.002 (0.977, 1.029)	0.993 (0.963, 1.025)	0.990 (0.956, 1.025)	0.991 (0.954, 1.030)
n-Dodecane	1.005 (0.979, 1.031)	1.005 (0.975, 1.037)	1.000 (0.966, 1.035)	1.013 (0.976, 1.052)
branched or cyclo- Alkanes				
Isobutane	1.018 (0.975, 1.064)	1.018 (0.968, 1.071)	1.016 (0.961, 1.074)	1.025 (0.965, 1.088)
Isopentane	1.021 (0.986, 1.058)	1.031 (0.990, 1.073)	1.032 (0.986, 1.079)	1.039 (0.990, 1.091)
2-Methylpentane	0.986 (0.955, 1.019)	0.976 (0.941, 1.013)	0.975 (0.936, 1.015)	0.990 (0.948, 1.034)
3-Methylpentane	0.997 (0.977, 1.018)	0.991 (0.967, 1.015)	0.985 (0.959, 1.012)	0.992 (0.963, 1.021)
3-Methylhexane	0.989 (0.961, 1.018)	0.982 (0.949, 1.017)	0.991 (0.953, 1.030)	1.018 (0.975, 1.062)
Cyclopentane	0.984 (0.963, 1.005)	0.989 (0.966, 1.013)	0.989 (0.964, 1.015)	0.996 (0.969, 1.023)
Cyclohexane	0.981 (0.949, 1.014)	0.957 (0.920, 0.996)	0.968 (0.926, 1.012)	1.017 (0.969, 1.068)
Methylcyclopentane	0.999 (0.961, 1.038)	0.980 (0.936, 1.026)	0.981 (0.932, 1.032)	1.019 (0.964, 1.078)
Methylcyclohexane	0.984 (0.950, 1.020)	0.970 (0.930, 1.011)	0.979 (0.933, 1.026)	1.017 (0.965, 1.071)

Substance	lag01	lag02	lag03	lag04
Alkenes/Alkynes				
Acetylene	0.997 (0.953, 1.043)	0.982 (0.934, 1.033)	0.966 (0.915, 1.020)	0.980 (0.924, 1.038)
Ethylene	1.004 (0.955, 1.055)	0.981 (0.926, 1.039)	0.980 (0.920, 1.044)	0.987 (0.922, 1.057)
Propylene	1.023 (0.978, 1.071)	1.003 (0.952, 1.057)	1.007 (0.951, 1.065)	1.001 (0.942, 1.063)
1-Butene	0.977 (0.948, 1.007)	0.972 (0.939, 1.005)	0.974 (0.939, 1.010)	0.981 (0.943, 1.020)
Aromatics				
Benzene	1.005 (0.957, 1.056)	0.999 (0.945, 1.055)	0.998 (0.941, 1.059)	1.016 (0.954, 1.083)
Ethylbenzene	0.996 (0.964, 1.029)	0.986 (0.950, 1.024)	0.995 (0.955, 1.038)	1.013 (0.968, 1.059)
Toluene	0.914 (0.879, 0.951)	0.887 (0.847, 0.930)	0.918 (0.871, 0.967)	0.992 (0.935, 1.051)
m/p-Xylene	0.986 (0.951, 1.022)	0.982 (0.942, 1.024)	0.993 (0.949, 1.040)	1.011 (0.962, 1.062)
o-Xylene	0.989 (0.954, 1.025)	0.979 (0.940, 1.021)	0.988 (0.944, 1.033)	1.001 (0.953, 1.051)
1,2,4-Trimethylbenzene	1.003 (0.976, 1.030)	0.989 (0.959, 1.020)	0.990 (0.957, 1.023)	1.001 (0.966, 1.038)

*p-value <0.05: statistically significant

Table S8. Relative Risk (95% CI) in hospital admissions and visits for asthma per IQR increase of VOC compounds by different single-day lags

Substance	lag0	lag1	lag2	lag3	lag4
***n*-Alkanes**					
Ethane	1.001 (0.964, 1.039)	1.000 (0.960, 1.042)	0.995 (0.956, 1.034)	0.995 (0.957, 1.034)	0.998 (0.962, 1.036)
Propane	1.036 (1.004, 1.069)*	0.967 (0.935, 1.000)	1.024 (0.991, 1.058)	0.973 (0.942, 1.004)	1.020 (0.989, 1.052)
n-Butane	1.036 (1.001, 1.071)*	0.972 (0.937, 1.008)	1.016 (0.981, 1.053)	0.969 (0.935, 1.004)	1.036 (1.002, 1.072)*
n-Pentane	1.011 (0.985, 1.038)	0.972 (0.945, 0.999)	1.037 (1.009, 1.065)*	0.995 (0.969, 1.022)	1.028 (1.003, 1.054)*
Hexane	1.000 (0.971, 1.031)	0.910 (0.882, 0.939)	1.022 (0.992, 1.053)	1.017 (0.987, 1.047)	1.068 (1.038, 1.098)*
n-Heptane	1.009 (0.991, 1.027)	0.971 (0.953, 0.990)	1.003 (0.985, 1.022)	1.009 (0.991, 1.027)	1.024 (1.006, 1.042)*
n-Octane	1.009 (0.990, 1.028)	0.972 (0.954, 0.991)	1.003 (0.984, 1.021)	1.009 (0.991, 1.028)	1.016 (0.998, 1.035)
n-Nonane	1.014 (0.998, 1.030)	0.979 (0.962, 0.996)	1.004 (0.988, 1.021)	1.002 (0.986, 1.018)	1.005 (0.990, 1.021)
n-Decane	1.019 (1.002, 1.035)*	0.960 (0.943, 0.977)	1.008 (0.991, 1.024)	0.992 (0.976, 1.008)	1.010 (0.994, 1.026)
n-Undecane	1.012 (0.996, 1.029)	0.979 (0.963, 0.997)	1.001 (0.985, 1.018)	0.991 (0.974, 1.008)	1.009 (0.993, 1.026)
n-Dodecane	1.007 (0.990, 1.024)	0.982 (0.965, 1.000)	1.007 (0.989, 1.025)	0.988 (0.970, 1.006)	1.023 (1.006, 1.040)*
branched and cyclo-Alkanes					
Isobutane	1.016 (0.986, 1.047)	0.991 (0.960, 1.023)	1.010 (0.979, 1.042)	0.985 (0.955, 1.016)	1.019 (0.990, 1.050)
Isopentane	1.021 (0.997, 1.046)	0.973 (0.948, 0.998)	1.023 (0.998, 1.049)	0.987 (0.963, 1.012)	1.018 (0.995, 1.042)
2-Methylpentane	1.018 (0.995, 1.042)	0.961 (0.938, 0.985)	1.002 (0.979, 1.026)	0.998 (0.975, 1.021)	1.027 (1.004, 1.050)*
3-Methylpentane	1.002 (0.987, 1.016)	0.977 (0.961, 0.992)	0.994 (0.979, 1.010)	0.996 (0.982, 1.012)	1.009 (0.995, 1.024)
3-Methylhexane	1.020 (1.003, 1.038)*	0.954 (0.937, 0.972)	1.015 (0.998, 1.033)	1.010 (0.993, 1.028)	1.034 (1.016, 1.052)*
Cyclopentane	0.998 (0.982, 1.014)	0.989 (0.972, 1.006)	1.006 (0.989, 1.023)	0.987 (0.97, 1.004)	1.010 (0.994, 1.026)
Cyclohexane	1.019 (0.998, 1.041)	0.953 (0.933, 0.974)	1.004 (0.983, 1.025)	1.013 (0.992, 1.033)	1.048 (1.028, 1.070)*
Methylcyclopentane	1.060 (1.034, 1.086)*	0.917 (0.894, 0.941)	1.018 (0.994, 1.043)	1.000 (0.977, 1.025)	1.047 (1.023, 1.072)*
Methylcyclohexane	1.005 (0.983, 1.027)	0.959 (0.938, 0.981)	1.005 (0.984, 1.027)	1.013 (0.992, 1.035)	1.039 (1.017, 1.061)*

Substance	lag0	lag1	lag2	lag3	lag4
Alkenes/Alkynes					
Acetylene	1.011 (0.979, 1.045)	0.949 (0.916, 0.983)	1.003 (0.968, 1.039)	0.953 (0.920, 0.988)	1.033 (1.000, 1.068)
Ethylene	1.018 (0.984, 1.052)	0.964 (0.930, 1.000)	0.986 (0.952, 1.022)	0.999 (0.965, 1.035)	1.012 (0.979, 1.046)
Propylene	1.012 (0.981, 1.045)	0.989 (0.957, 1.022)	0.977 (0.946, 1.010)	1.006 (0.974, 1.039)	0.993 (0.962, 1.025)
1-Butene	0.991 (0.969, 1.014)	0.971 (0.948, 0.994)	0.996 (0.973, 1.019)	0.991 (0.969, 1.014)	0.996 (0.975, 1.019)
Aromatics					
Benzene	1.030 (0.993, 1.068)	0.950 (0.914, 0.988)	1.013 (0.975, 1.052)	0.985 (0.949, 1.023)	1.032 (0.996, 1.069)
Ethylbenzene	1.019 (0.998, 1.040)	0.966 (0.944, 0.987)	1.010 (0.989, 1.032)	1.005 (0.985, 1.026)	1.023 (1.003, 1.043)*
Toluene	1.011 (0.985, 1.037)	0.884 (0.860, 0.907)	1.017 (0.991, 1.043)	1.011 (0.986, 1.036)	1.070 (1.045, 1.095)*
m/*p*-Xylene	1.008 (0.985, 1.031)	0.963 (0.940, 0.987)	1.009 (0.986, 1.032)	1.002 (0.979, 1.025)	1.021 (0.998, 1.043)
o-Xylene	1.008 (0.985, 1.032)	0.963 (0.940, 0.987)	1.002 (0.979, 1.026)	0.999 (0.976, 1.023)	1.020 (0.997, 1.043)
1,2,4-Trimethylbenzene	1.016 (0.999, 1.033)	0.966 (0.949, 0.984)	1.001 (0.984, 1.018)	1.001 (0.984, 1.018)	1.014 (0.997, 1.031)

*p-value <0.05: statistically significant

Table S9. Relative Risk (95% CI) in hospital admissions and visits for asthma per IQR increase of VOC compounds by different moving-average lags

Substance	lag01	lag02	lag03	lag04
***n*-Alkanes**				
Ethane	1.005 (0.960, 1.052)	1.000 (0.949, 1.055)	1.002 (0.945, 1.063)	1.004 (0.942, 1.070)
Propane	1.010 (0.972, 1.050)	1.016 (0.972, 1.062)	1.009 (0.961, 1.060)	1.021 (0.968, 1.077)
n-Butane	1.013 (0.973, 1.054)	1.016 (0.971, 1.063)	1.010 (0.961, 1.061)	1.028 (0.974, 1.084)
n-Pentane	0.993 (0.963, 1.025)	1.015 (0.979, 1.052)	1.030 (0.990, 1.073)	1.051 (1.006, 1.098)*
Hexane	0.926 (0.893, 0.959)	0.937 (0.899, 0.976)	0.972 (0.929, 1.017)	1.019 (0.970, 1.070)
n-Heptane	0.985 (0.963, 1.008)	0.988 (0.961, 1.015)	1.001 (0.971, 1.031)	1.019 (0.986, 1.053)
n-Octane	0.985 (0.962, 1.008)	0.987 (0.960, 1.015)	1.001 (0.969, 1.033)	1.016 (0.981, 1.052)
n-Nonane	0.995 (0.975, 1.016)	0.998 (0.974, 1.022)	1.001 (0.974, 1.028)	1.005 (0.976, 1.034)
n-Decane	0.982 (0.962, 1.003)	0.986 (0.963, 1.010)	0.984 (0.959, 1.011)	0.991 (0.963, 1.019)
n-Undecane	0.992 (0.971, 1.014)	0.992 (0.967, 1.018)	0.987 (0.958, 1.016)	0.992 (0.961, 1.024)
n-Dodecane	0.990 (0.969, 1.013)	0.993 (0.968, 1.019)	0.988 (0.959, 1.017)	1.003 (0.971, 1.036)
branched or cyclo-Alkanes				
Isobutane	1.011 (0.975, 1.049)	1.015 (0.973, 1.059)	1.016 (0.970, 1.065)	1.030 (0.980, 1.084)
Isopentane	1.000 (0.971, 1.030)	1.010 (0.977, 1.045)	1.012 (0.975, 1.051)	1.024 (0.983, 1.066)
2-Methylpentane	0.984 (0.956, 1.011)	0.983 (0.952, 1.015)	0.991 (0.956, 1.026)	1.008 (0.971, 1.047)
3-Methylpentane	0.978 (0.960, 0.995)	0.971 (0.951, 0.991)	0.971 (0.949, 0.993)	0.978 (0.954, 1.002)
3-Methylhexane	0.980 (0.957, 1.003)	0.992 (0.964, 1.020)	1.012 (0.980, 1.045)	1.044 (1.008, 1.081)*
Cyclopentane	0.988 (0.970, 1.006)	0.989 (0.970, 1.009)	0.986 (0.965, 1.007)	0.989 (0.967, 1.012)
Cyclohexane	0.975 (0.949, 1.001)	0.975 (0.945, 1.007)	1.002 (0.966, 1.039)	1.047 (1.006, 1.089)*
Methylcyclopentane	0.978 (0.947, 1.010)	0.985 (0.949, 1.022)	1.002 (0.961, 1.045)	1.042 (0.996, 1.091)
Methylcyclohexane	0.967 (0.939, 0.995)	0.973 (0.940, 1.006)	0.995 (0.957, 1.035)	1.030 (0.987, 1.075)

Substance	lag01	lag02	lag03	lag04
Alkenes/Alkynes				
Acetylene	0.957 (0.923, 0.992)	0.947 (0.910, 0.987)	0.936 (0.895, 0.978)	0.948 (0.904, 0.993)
Ethylene	0.984 (0.946, 1.024)	0.971 (0.927, 1.017)	0.977 (0.928, 1.029)	0.987 (0.934, 1.044)
Propylene	0.997 (0.960, 1.036)	0.984 (0.942, 1.027)	0.988 (0.943, 1.036)	0.988 (0.939, 1.039)
1-Butene	0.959 (0.934, 0.985)	0.957 (0.929, 0.986)	0.956 (0.925, 0.988)	0.958 (0.926, 0.992)
Aromatics				
Benzene	0.988 (0.949, 1.028)	0.992 (0.949, 1.037)	0.996 (0.949, 1.045)	1.010 (0.960, 1.063)
Ethylbenzene	0.988 (0.963, 1.014)	0.993 (0.964, 1.022)	1.006 (0.974, 1.040)	1.024 (0.988, 1.061)
Toluene	0.900 (0.872, 0.929)	0.903 (0.870, 0.937)	0.945 (0.905, 0.986)	1.011 (0.964, 1.060)
m/p-Xylene	0.977 (0.949, 1.006)	0.982 (0.950, 1.016)	0.992 (0.956, 1.029)	1.007 (0.968, 1.048)
o-Xylene	0.974 (0.946, 1.003)	0.974 (0.941, 1.007)	0.980 (0.944, 1.017)	0.992 (0.953, 1.033)
1,2,4-Trimethylbenzene	0.987 (0.966, 1.008)	0.986 (0.962, 1.010)	0.992 (0.966, 1.019)	1.000 (0.972, 1.029)

*p-value <0.05: statistically significant

Table S10. Relative Risk (95% CI) in hospital admissions and visits for AD per quartile increase of WQS index by different moving-average lags

Substance	lag0	lag01	lag02	lag03	lag04
n-Alkanes	1.036 (0.976, 1.100)	0.998 (0.971, 1.025)	0.990 (0.959, 1.023)	0.996 (0.962, 1.031)	0.993 (0.958, 1.028)
branched or cyclo-Alkanes	1.048 (1.028, 1.068)*	1.007 (0.985, 1.028)	0.992 (0.963, 1.021)	0.986 (0.958, 1.015)	1.003 (0.976, 1.031)
Alkenes/Alkynes	1.034 (0.989, 1.081)	1.008 (0.983, 1.034)	0.971 (0.937, 1.006)	0.973 (0.943, 1.004)	0.980 (0.949, 1.013)
Aromatics	0.993 (0.928, 1.062)	0.979 (0.958, 1.000)	0.980 (0.949, 1.012)	0.980 (0.957, 0.957)	0.998 (0.973, 1.023)

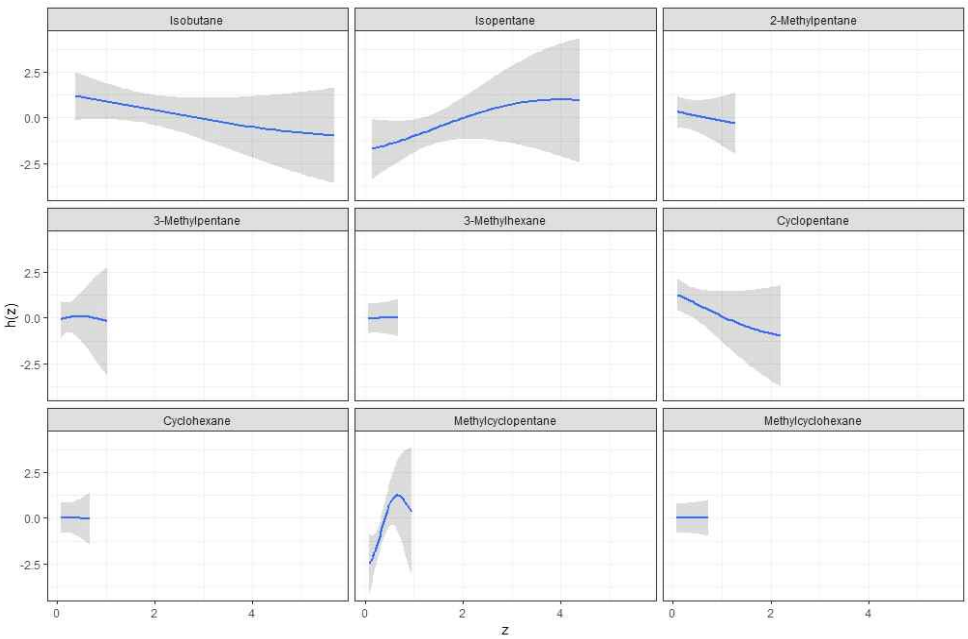
*p-value <0.05: statistically significant

Table S11. Relative Risk (95% CI) in hospital admissions and visits for asthma per quartile increase of WQS index by different moving-average lags

Substance	lag0	lag01	lag02	lag03	lag04
n-Alkanes	1.051 (0.989, 1.116)	1.000 (0.974, 1.026)	1.005 (0.978, 1.033)	1.020 (0.992, 1.049)	1.021 (0.989, 1.054)
branched or cyclo-Alkanes	1.033 (1.013, 1.053)*	0.998 (0.980, 1.016)	0.990 (0.967, 1.014)	1.005 (0.979, 1.030)	1.028 (1.007, 1.050)*
Alkenes/Alkynes	1.002 (0.979, 1.025)	0.989 (0.967, 1.012)	0.970 (0.942, 0.998)	0.974 (0.944, 1.004)	0.993 (0.961, 1.025)
Aromatics	1.014 (0.993, 1.037)	0.977 (0.959, 0.995)	0.988 (0.964, 1.013)	0.993 (0.967, 1.020)	1.013 (0.985, 1.041)

*p-value <0.05: statistically significant

(A)



(B)

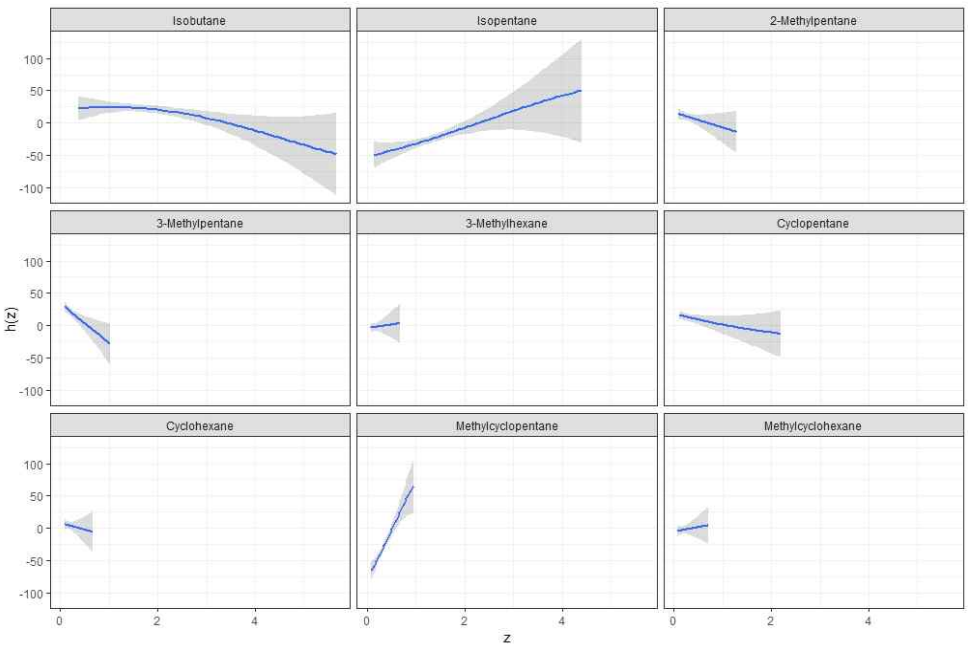
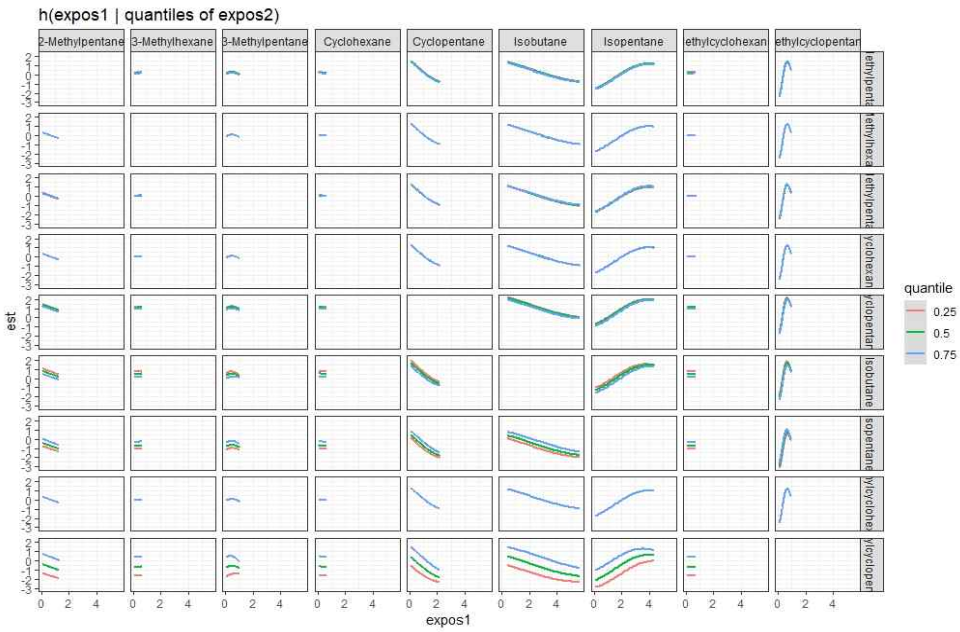


Figure S7. Univariate exposure-response relationship between each VOC concentration in branched or cyclo-Alkanes and estimates of AD (A) and asthma (B) at lag 0. Estimates and 95% CI bands for each VOC with other VOCs are fixed at their 50th percentile.

(A)



(B)

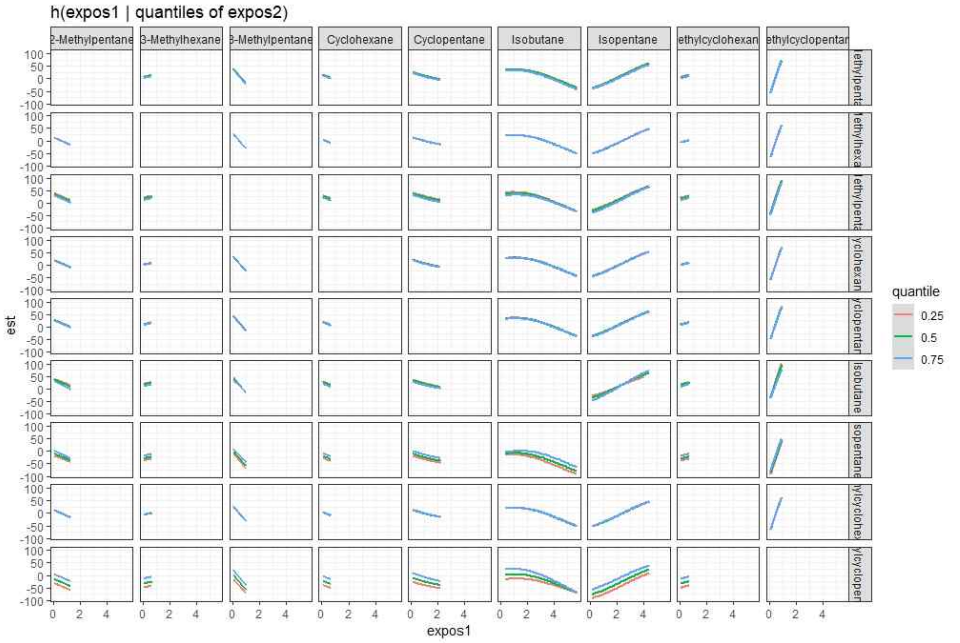


Figure S8. Bivariate exposure-response relationship between each VOC concentration in branched or cyclo-Alkanes and estimates of AD (A) and asthma (B) at lag 0. Each VOC presented on the upper coordinate axis and estimates when the corresponding VOCs on the right longitudinal are axis fixed at the 25th, 50th, and 75th percentiles and the remaining VOCs in each group are held at the 50th percentiles.

Table S12. Prevalence case (prevalence per 100,000 population) of AD under age of 19, during 2015-2019

	2015	2016	2017	2018	2019
Total	3,623 (220)	3,548 (225)	3,502 (232)	3,139 (218)	2,947 (215)
Age group					
0-2	1,120 (483)	1,101 (495)	1,054 (511)	734 (402)	462 (280)
3-6	1,058 (336)	968 (314)	938 (314)	960 (333)	1,050 (383)
7-12	948 (199)	976 (213)	971 (215)	903 (201)	883 (197)
13-18	497 (80)	503 (86)	539 (97)	542 (105)	552 (114)
Sex					
Male	1,957 (231)	1,961 (242)	1,958 (252)	1,715 (232)	1,633 (232)
Female	1,666 (209)	1,587 (208)	1,544 (211)	1,424 (204)	1,314 (197)

Table S13. Prevalence case (prevalence per 100,000 population) of asthma under age of 19, during 2015-2019

	2015	2016	2017	2018	2019
Total	10,950 (665)	12,893 (818)	11,457 (759)	11,289 (785)	10,332 (754)
Age group					
0-2	2,986 (1,287)	3,861 (1,734)	3,670 (1,781)	3,124 (1,709)	1,806 (1,094)
3-6	4,209 (1,337)	4,430 (1,439)	3,924 (1,315)	4,330 (1,502)	4,453 (1,626)
7-12	2,863 (602)	3,422 (745)	2,812 (623)	2,724 (608)	2,859 (637)
13-18	892 (143)	1,180 (201)	1,051 (190)	1,111 (214)	1,214 (252)
Sex					
Male	6,227 (734)	7,246 (892)	6,470 (832)	6,357 (860)	5,856 (831)
Female	4,723 (592)	5,647 (739)	4,987 (680)	4,932 (707)	4,476 (672)

Table S14. The average duration of days of care for AD under age of 19, during 2015-2019

(Unit: days)

	2015	2016	2017	2018	2019
Outpatient	7.1	8.9	9.0	10.4	8.7
Inpatient	4.2	4.3	4.4	4.6	4.7
Average	**4.2**	**4.3**	**4.5**	**4.6**	**4.7**

Table S15. The average duration of days of care for asthma under age of 19, during 2015-2019

(Unit: days)

	2015	2016	2017	2018	2019
Outpatient	17.3	16.5	14.0	12.2	11.6
Inpatient	7.2	7.3	7.4	7.4	7.0
Average	**7.4**	**7.5**	**7.5**	**7.5**	**7.1**

Table S16. The average duration of inpatient admissions and outpatient visits for AD under age of 19, during 2015-2019

(Unit: days)

	2015	2016	2017	2018	2019
Outpatient	4.2	4.3	4.4	4.6	4.7
Inpatient	7.3	6.5	7.2	6.2	6.4
Average	**4.2**	**4.3**	**4.5**	**4.6**	**4.7**

Table S17. The average duration of inpatient admissions and outpatient visits for asthma under age of 19, during 2015-2019

(Unit: days)

	2015	2016	2017	2018	2019
Outpatient	7.2	7.3	7.3	7.4	7.0
Inpatient	12.7	12.0	11.3	10.2	9.4
Average	**7.4**	**7.5**	**7.4**	**7.5**	**7.1**

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