HHS Public Access

Author manuscript

Epidemiology. Author manuscript; available in PMC 2018 March 01.

Published in final edited form as:

Epidemiology. 2017 March ; 28(2): 197–206. doi:10.1097/EDE.0000000000000607.

Estimating acute cardiorespiratory effects of ambient volatile organic compounds

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Abstract

Background—The health effects of ambient volatile organic compounds (VOCs) have received less attention in epidemiologic studies than other commonly measured ambient pollutants. In this study, we estimated acute cardiorespiratory effects of ambient VOCs in an urban population.

Methods—Daily concentrations of 89 VOCs were measured at a centrally-located ambient monitoring site in Atlanta and daily counts of emergency department visits for cardiovascular diseases and asthma in the 5-county Atlanta area were obtained for the 1998–2008 period. To understand the health effects of the large number of species, we grouped these VOCs *a priori* by chemical structure and estimated the associations between VOC groups and daily counts of emergency department visits in a time-series framework using Poisson regression. We applied three analytic approaches to estimate the VOC group effects: an indicator pollutant approach, a joint effect analysis, and a random effect meta-analysis, each with different assumptions. We performed sensitivity analyses to evaluate co-pollutant confounding.

Results—Hydrocarbon groups, particularly alkenes and alkynes, were associated with emergency department visits for cardiovascular diseases, while the ketone group was associated with emergency department visits for asthma.

Conclusions—The associations observed between emergency department visits for cardiovascular diseases and alkenes and alkynes, may reflect the role of traffic exhaust, while the association between asthma visits and ketones may reflect the role of secondary organic compounds. The different patterns of associations we observed for cardiovascular diseases and asthma suggest different modes of action of these pollutants or the mixtures they represent.

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Description of conflicts of interest, or statement that there is no conflict of interest: We have no conflicts of interest to declare.

INTRODUCTION

Ambient air pollution is a complex mixture of particulate matter varying in size and composition and gaseous pollutants. Health effects of particulate matter, its constituents, and criteria gases have been frequently investigated.[1, 2] Other coexisting pollutants, for example volatile organic compounds (VOCs), have received less attention in epidemiologic studies.

Organic pollutants include a variety of compounds, such as hydrocarbons, halocarbons, and oxygenates. These compounds reside in the vapor phase, particle phase, or both, depending on organic equilibrium properties (e.g., vapor pressure) and particle surface composition (e.g., water content). There is a dynamic continuum among VOCs, semi-volatile organic compounds (SVOCs), and particle phase organics, and together they constitute total organic aerosol.[3, 4] There is increasing evidence for the health effects of organic aerosols. Epidemiologic studies have suggested cardiorespiratory effects of mixtures from fossil fuel combustion, which contain large fractions of organic pollutants.[4] Ambient fine particle organic carbon ($PM_{2.5}$ OC) and its constituents have been associated with various cardiorespiratory health outcomes.[4–13] VOCs may also have an impact on health. Previous epidemiologic studies have suggested respiratory effects of indoor VOCs.[14] Controlled human exposure studies have suggested inflammatory effects of VOCs.[15, 16] However, epidemiologic evidence on cardiorespiratory effects of ambient VOCs is sparse.[17–25] Most previous studies considered only a limited number of species and are not representative of the wide range of compounds found in urban air.

To advance our understanding of the health relevance of ambient VOCs, we estimated their acute cardiorespiratory effects in the Atlanta, Georgia, metropolitan population. This analysis capitalizes on our ongoing Study of Particles and Health in Atlanta (SOPHIA), which has information on ambient air pollution, including a wide range of VOCs, and emergency department visits.[26–29] To seek coherence in understanding the health effects of a large number of VOCs, we grouped VOCs *a priori* by chemical structure and estimated the group effects. Grouping by chemical structure was motivated by several considerations: 1) as chemical structure determines the reactivity of a compound, pollutants sharing a common chemical structure may be similar in toxicity, so grouping by chemical structure may enhance the understanding of their health associations from a biological perspective; and 2) pollutants sharing a common chemical structure may be generated from common emission sources or atmospheric chemical processes, so grouping by chemical structure may suggest health effects of these sources or processes.

While we grouped these VOCs by shared characteristics, pollutants within a group may still differ in their health associations and be subject to different levels of measurement error. As there is little understanding of the nature of these variations, we applied three analytic approaches to estimate the group effects, each with different assumptions concerning the variations within a group.

METHODS

VOC measurements and formation of VOC groups

Daily 24-hour average concentrations of VOCs were measured at the Atlanta Jefferson Street ambient monitoring site during 8/14/1998-12/31/2008 as part of the Aerosol Research and Inhalation Epidemiology Study (ARIES). Sampling details were previously published by Hansen *et al.*[30] Briefly, 24-hour samples were collected in evacuated 6-L passivated stainless canisters and then analyzed via gas-chromatography with flame ionization detection. Data included daily concentrations of 89 identified individual species (77 hydrocarbons and 12 oxygenates), total identified hydrocarbons, and total identified oxygenates (Supplement, eTable 1). Concentrations were reported in part per billion, as carbon (ppb-C), and the limit of detection (LOD) for all species was 0.1 ppb-C.

We grouped individual VOCs *a priori* by chemical structure. Groups among the 77 hydrocarbons included alkanes, alkenes, alkynes, and aromatic hydrocarbons, and among the 12 oxygenates included aldehydes, acids, ketones, and ethers. We further divided the alkanes into four groups (n-alkane, iso/anteiso-alkane, other branched alkane, cycloalkane) based on branching. For this analysis, we only included species with concentrations above the LOD on at least 90% of days. This left 46 species in seven hydrocarbon groups (n-alkane, iso/anteiso-alkane, other branched alkane, cycloalkane, alkene, alkyne, and aromatic) and three oxygenate groups (aldehyde, acid, and ketone) (Table 1). Observations below LOD were replaced with half the detection limit (0.05 ppb-C).

Emergency department visits

We obtained daily counts of emergency department visits for cardiovascular diseases and asthma among patients living within the five-county Atlanta area (Clayton, Cobb, DeKalb, Fulton, and Gwinnett) during 8/14/1998-12/31/2008. Daily counts of emergency department visits were aggregated from individual-level billing records from metropolitan Atlanta hospitals as part of SOPHIA.[26–29] We identified emergency department visits for cardiovascular diseases as those with primary International Classification of Diseases, 9th Revision (ICD-9) diagnosis codes for ischemic heart disease (410–414), cardiac dysrhythmias (427), congestive heart failure (428), or peripheral vascular and cerebrovascular disease (433–437, 440, 443–445, 451–453). Asthma visits were identified as those with primary ICD-9 diagnosis codes for asthma (493) or wheeze (786.09, before 10/1/1998; 786.07, after 10/1/1998). We used these emergency department data in accordance with agreements with the hospitals and the Georgia Hospital Association. This study was approved by the Emory University Institutional Review Board.

Analytic approaches

We first estimated the effects of total identified hydrocarbons and total identified oxygenates, and then estimated VOC group effects using three analytic approaches. All analyses were conducted in a time-series framework, in which we estimated the associations between daily levels of VOCs and daily counts of emergency department visits using Poisson regression accounting for over-dispersion. Based on our previous research on ambient air pollution and emergency department visits in Atlanta,[26–29] and studies on

ambient VOC health effects in other cities,[22, 24] we used same-day (lag 0) pollution levels in models predicting emergency department visits for cardiovascular diseases and 3-day moving average (of lags 0, 1, and 2) pollution levels in models predicting emergency department visits for asthma. All models included the same covariate control for temporal trends and meteorology: time splines with monthly knots, cubic function of same-day maximum temperature, cubic function of lag 1–2-day moving average minimum temperature (when using 3-day moving average pollution levels), cubic function of mean dew point temperature (same-day or 3-day moving average, matching the temporal metric of the pollution term), day of week, indicators for holidays, seasons, season-maximum temperature interaction, season-day of week interaction, and indicators for hospital participation periods. The estimated associations were reported as rate ratios per interquartile range (IQR) increase in pollutant concentrations.

Analyses of emergency department visits for cardiovascular diseases included all ages. For asthma visits, we performed analyses among all ages, and analyses stratified by age category (5–18 and 19+ years old), given our previous work suggesting that effects of air pollution on asthma may differ for children.[31]

Estimation of total VOC effects— We used single-pollutant models to estimate the effect of total identified hydrocarbons and total identified oxygenates, as follows:

$$\mathrm{Log}[\mathrm{E}(\mathrm{Y})]=\beta_0+\beta_1*(\mathrm{total})+\mathrm{covariate\ \ control} \quad \text{Eq. 1}$$

where Y was the daily count of emergency department visits for cardiovascular diseases or asthma, and *total* was the daily concentration of the total identified hydrocarbons or the total identified oxygenates.

Estimation of VOC group effects— We estimated VOC group effects using three analytic approaches: an indicator pollutant approach, a joint effect analysis, and a random effect meta-analysis.

1. Indicator pollutant approach: Pollutants in the same group may not be equally well measured. To minimize the impact of instrument measurement error on health effect estimation, we selected the pollutant with the highest median/LOD ratio as the indicator pollutant for each group, and considered the effect of the indicator pollutant as the group effect. This approach is based on the assumption that the pollutant with the concentration distribution furthest from the LOD is less prone to instrument-related measurement error. The effects of indicator pollutants were estimated using single-pollutant models as follows:

$$\mathrm{Log}[\mathrm{E}(\mathrm{Y})]=\beta_0+\beta_g*(\mathrm{indicator\ \ pollutant\ \ of\ \ group}_g)+\mathrm{covariate\ \ control} \quad \text{Eq 2.}$$

where *indicator pollutant of group*$_g$ was the concentration of the indicator pollutant for group g.

2. Joint effect analysis: The effect of a given indicator pollutant may not fully represent the effect of its group if pollutant effects within a group differ. To capture the contribution of different pollutants within a group, we estimated a joint effect per IQR increase in all pollutants of a group as follows:

$$\mathrm{Log}[\mathrm{E}(\mathrm{Y})]=\beta_0+\sum_{i=1}^{i=\mathrm{n_g}}\beta_\mathrm{i}*(\mathrm{pollutant}_i)+\mathrm{covariate\ \ control} \quad \text{Eq 3.}$$

where n_g is the number of pollutants in group g, and $pollutant_i$ represented the concentration of each pollutant in group g. The estimated joint effect of group g was calculated as $e^{\sum_{i=1}^{i=n_g} IQR_i*\hat{\beta}_i}$, where IQR_i was the interquartile range of $pollutant_i$ in group g.[32]

3. Random effect meta-analysis: In the joint effect analysis, we considered the individual pollutant effects as fixed, and estimated a combined effect per increase in all pollutants in a group. In this random effect meta-analysis, we considered pollutant effects within a group as random (normally distributed) and estimated the group mean as the group effect. We applied a two-stage regression to estimate the group means and the within-group variance.[33–35]

In the first stage, we included all 46 VOCs in the Poisson model as follows:

$$\mathrm{Log}[\mathrm{E}(\mathrm{Y})]=\beta_0+\sum_{i=1}^{i=46}\beta_i*(\mathrm{pollutant}_i)+\mathrm{covariate\ \ control} \quad \text{Eq 4.}$$

where $pollutant_i$ represented the concentration of each of the 46 VOCs. We obtained the estimated pollutant effects and their estimated variance-covariance matrix from the first stage model.

Let $\hat{\boldsymbol{\beta}}$ denote the vector of the estimated pollutant effects per IQR increase in pollutant concentrations, and let $\hat{\mathbf{V}}$ denote the corresponding variance–covariance matrix. In the second stage, we regressed the first stage estimates against indicator variables representing the groups:

$$\hat{\boldsymbol{\beta}}=\mathrm{Z}\alpha+\boldsymbol{\theta}+\varepsilon \quad \text{Eq 5.}$$

where $\mathbf{Z}$ is the design matrix indexing the grouping; $\boldsymbol{\alpha}$ is a vector of the group means; $\boldsymbol{\theta}$ is a vector of pollutant-specific deviation from its group mean with $\boldsymbol{\theta} \sim \mathrm{N}(0, \boldsymbol{\tau}^2\boldsymbol{I})$, where $\boldsymbol{\tau}^2$ is within group variance, and $\boldsymbol{\varepsilon}$ is the estimation error with $\boldsymbol{\varepsilon} \sim \mathrm{N}(0, \hat{\mathbf{V}})$.

We estimated the group means and within-group variance under a Bayesian framework using Markov chain Monte Carlo. Prior distributions for the group means and the within-group variance $\boldsymbol{\tau}^2$ were normal with dispersed variance and inverse-gamma (0.001, 0.001), respectively.

Sensitivity analyses—We performed a series of sensitivity analyses for the indicator pollutant approach, using emergency department visits among all ages. First, we evaluated

model misspecification by estimating the associations between tomorrow's pollutant levels (lag negative 1) and today's emergency department visits, controlling for today's pollutant and covariate levels. Tomorrow's pollutant levels should not be associated with today's emergency department visits in the absence of confounding, measurement error, or other model misspecification, as cause must precede effect.[36] Second, we evaluated potential confounding by VOCs, where we estimated the effect of each VOC group conditioning on others by including the 10 VOC indicator pollutants in one model. Third, we evaluated potential confounding by selected major pollutants by controlling for them one at a time in each VOC indicator pollutant model. The major pollutants considered in this analysis included 24-hour average $PM_{2.5}$ OC, one-hour maximum carbon monoxide (CO), one-hour maximum nitrogen dioxide (NO_2), and eight-hour maximum ozone (O_3). These pollutants were also measured at the Atlanta Jefferson Street ambient monitor during the study period.[30]

RESULTS

Descriptive statistics and grouping information for the 46 VOCs included in the analysis are listed in Table 1, and their Pearson correlations are listed in Supplementary eTable 2. Hydrocarbons had moderate-to-strong positive correlations with one another (r from 0.48 to 0.98, with mean of 0.82). Oxygenates had weak-to-moderate positive correlations with one another (r from 0.20 to 0.64, with mean of 0.42). Correlations between hydrocarbons and oxygenates were weak-to-moderate (r from –0.32 to 0.67, with mean of 0.28).

Descriptive statistics of the major pollutants ($PM_{2.5}$ OC, CO, NO_2, and O_3) considered in the sensitivity analysis are listed in Table 1, and their correlations with the 46 VOCs are listed in the Supplement eTable 3. Hydrocarbons had moderate-to-strong positive correlations with $PM_{2.5}$ OC, CO, and NO_2 (r from 0.40 to 0.76, with mean of 0.60), while weak correlations with O_3 (r from –0.26 to 0.23, with mean of 0.10). Oxygenates had weak-to-moderate correlations with these major pollutants (r from –0.03 to 0.57, with mean of 0.22).

During the study period, there were 251,030 emergency department visits for cardiovascular diseases- (66 per day) and 233,121 emergency department visits for asthma (61 per day overall; 18 per day among 5–18 year olds; and 27 per day among 19+ year olds).

Primary analysis—We first estimated associations between total VOCs and emergency department visits using single-pollutant models. For emergency department visits of cardiovascular diseases, $\widehat{RR}$ (95% CI) per IQR increase in total hydrocarbons and in total oxygenates were 1.005 (1.001, 1.009) and 1.004 (0.996, 1.013), respectively. For asthma visits among all ages, the association for total oxygenates was stronger than that for total hydrocarbons, with $\widehat{RR}$s (95% CI) of 1.008 (1.001, 1.015) and 1.024 (1.007, 1.041), respectively. We observed this pattern among 5–18 and 19+ year olds as well (Supplement, eTable 4).

We then estimated VOC group effects using the three analytic approaches (Table 2). Note that the alkyne, acid, and ketone groups included only one pollutant, and thus their joint effect estimates were the same as their indicator pollutant effect estimates. For emergency

department visits of cardiovascular diseases, $\widehat{RRs}$ per IQR increase in hydrocarbon groups were generally similar to one another when estimated using the indicator pollutant approach and the joint effect analysis. However, in the random effect meta-analysis, only the alkyne group was associated with emergency department visits of cardiovascular diseases, with a $\widehat{RR}$ (95% CI) of 1.007 (1.001, 1.012). Among oxygenates, associations with cardiovascular diseases were generally consistent with the null except for the aldehyde group in the joint effects analysis (Table 2).

For asthma visits among all ages, the association with the ketone group was the largest, with $\widehat{RRs}$ per IQR increase of 1.026 (1.004, 1.048) using the indicator pollutant approach, 1.026 (1.004, 1.048) in the joint effect analysis, and 1.024 (1.000, 1.049) in the random effect meta-analysis. The association for the aldehyde group was also large in the joint effect analysis, with a $\widehat{RR}$ (95% CI) of 1.021 (1.004, 1.037). In comparison, the associations for hydrocarbon groups were weaker (Table 2). We observed this pattern of associations within the 5–18 and 19+ year age categories as well (Supplement, eTable 5). The biggest difference between these two age categories was that the association for the acid group was stronger among 5–18 than 19+ year olds.

Sensitivity analysis—We performed sensitivity analyses using emergency department visits among all ages. For the indicator pollutant approach, we found associations between emergency department visits of cardiovascular diseases and tomorrow's levels for the acid and ketone groups, and between asthma visits and tomorrow's levels for the alkyne group, suggesting possible model misspecification when estimating these associations. Other associations with tomorrow's pollutant levels were consistent with the null, as expected under a well-specified model (Table 3).

We estimated the association for each VOC group conditioning on others by including the 10 VOC indicator pollutants in one model. The estimated associations between emergency department visits of cardiovascular diseases and the alkene and alkyne groups had little change compared to those in the primary analysis using the indicator pollutant approach, while the estimated associations for other hydrocarbon groups were closer to the null (Table 3). For asthma visits, results of this sensitivity analysis appeared to be unstable.

We estimated the association for each VOC indicator pollutant controlling for major pollutants one at a time in two-pollutant models. The estimated associations between emergency department visits for cardiovascular diseases and hydrocarbon groups were weaker when controlling for CO; the associations for CO were also weaker in two-pollutant models with the alkene or alkyne groups, compared to its estimated association in a single-pollutant model (Table 4). The estimated associations between asthma visits and the oxygenate groups had little change when controlling for any of these major pollutants, and $\widehat{RRs}$ per IQR increase in the ketone group were the largest ($\widehat{RRs}$ from 1.025 to 1.027). The associations between asthma visits and hydrocarbon groups, on the other hand, were weaker when controlling for OC, CO, or NO_2 (Table 5).

DISCUSSION

In this study, we estimated acute cardiorespiratory effects of ambient VOCs by grouping these compounds based on chemical structure and estimating VOC group effects. Because few epidemiologic studies have examined the health effect of ambient VOCs, there is little understanding of the variation of pollutant effects and measurement error within a group, confounding by VOCs, and confounding by other fractions of air pollution. Because of these challenges, we applied multiple analytic approaches to estimate VOC group effects, and performed a range of sensitivity analyses.

We used the indicator pollutant approach as an attempt to minimize the instrument measurement error by using what we believed to be the best-measured pollutant. In the joint effect analysis, we considered individual pollutant effects as fixed and estimated a combined effect per increment of all pollutants in a group. In the random effect meta-analysis, we considered individual pollutant effects as random (normally distributed within a group) and estimated the group mean effect. Any inconsistency among group effect estimates using these approaches does not necessarily indicate that any of the estimates are wrong, but could reflect that these approaches define the group effects differently.

In our primary analysis of emergency department visits for cardiovascular diseases, we observed similar associations across hydrocarbon groups when using the indicator pollutant approach (Table 2). We performed a sensitivity analysis to estimate the effect of each group conditioning on others, and the results suggested that many of the hydrocarbon groups might be surrogates of the alkene and the alkyne groups (Table 3). The finding of alkynes being associated with cardiovascular diseases conditioning on other VOC groups agreed with the random effect meta-analysis results in the primary analysis, in which the estimated associations for each group were adjusted for others (Table 2).

However, it is also possible that these VOC groups are surrogates for other pollutants in the ambient air, and that the alkene and the alkyne groups in our analysis were merely better surrogates than other VOCs. To understand what the VOCs might be surrogates for, we performed an additional sensitivity analysis controlling for selected major pollutants one at a time in each VOC indicator pollutant model. When controlling for CO, the estimated associations between cardiovascular visits and the alkene and the alkyne groups were weaker, and the CO association was also weaker (Table 4). The alkene and the alkyne groups may be part of a causal mixture with CO, or, these pollutants could all be surrogates of other unmeasured pollutants in the causal mixture. Considering that pollutants in the alkene and alkyne groups are mainly generated from combustion, among which acetylene (the pollutant in the alkyne group) is a marker of automobile emissions, and CO is a classic traffic marker, their associations with cardiovascular diseases may reflect the effect of traffic exhaust.

In our primary analysis of asthma visits, we observed relatively strong associations with the ketone group among all ages (Table 2) and among specific age categories (Supplement, eTable 5). We performed sensitivity analyses on asthma visits of all ages, and found that the estimated associations for the ketone group had little change after controlling for any of the major pollutants (Table 5). While certain ketones are byproducts of ozone formation, and the pollutant in our ketone group is moderately correlated with ozone in this analysis, the

association between ketone and asthma visits had little change after controlling for ozone. The association between ketone and asthma visits could reflect something beyond the effect of ozone: perhaps, the effect of other secondary organic compounds that are also generated through atmospheric oxidation processes.

Overall, we found that hydrocarbon groups, particularly the alkene and alkyne groups, were associated with emergency department visits for cardiovascular diseases, while the ketone group was associated with asthma visits. Some hydrocarbon groups were associated with asthma visits, however, the magnitudes of their associations were smaller compared to the ketone group. The different patterns of associations we observed for the cardiovascular diseases and asthma suggest there could be different modes of action of these pollutants or the pollution mixtures they represent. The hydrocarbons included in our analysis are primarily emitted from traffic or other combustion sources, while oxygenates such as ketones are largely secondary. Previous studies of particle-phase pollutants have suggested that secondary organic compounds are more related to respiratory inflammation, as they are hydrophilic and thus more readily react with constituents in the respiratory tract,[6] while primary organic compounds are more related to systemic inflammation.[6, 7, 37] Our results on vapor-phase organics are consistent with these previous findings on particle-phase pollutants.

Previous epidemiologic studies reported positive associations between cardiovascular health outcomes and ambient hydrocarbons.[23, 25] Our finding of the alkyne group being associated with cardiovascular health outcomes has not been reported previously, although Suh *et al.* combined alkyne with other VOCs in a combustible category and reported its positive association with cardiovascular hospital admission.[35] Our findings on asthma and ambient VOCs are supported by existing evidence in general. Previous epidemiologic studies reported positive associations between respiratory health outcomes and ambient hydrocarbons, aldehydes, and ketones.[17–19, 21, 22, 24] Among them, Delfino *et al.* showed in a panel of asthmatic children that aldehyde (formaldehyde) and ketone (acetone) were associated with severe asthma symptoms with greater magnitudes compared to hydrocarbons (benzene, toluene, and xylenes),[19] similar to the pattern we observed here.

Our results are subject to spatial misalignment and instrument measurement error. The degree of these sources of error likely differs by VOC group, and thus the estimated group effects should be compared in light of these limitations. Compared to oxygenates, hydrocarbons as primary pollutants may be more subject to spatial misalignment, due to larger spatially heterogeneity. If this is the case, the estimated associations for hydrocarbon groups may be more biased towards the null compared to those for the oxygenate groups. Additionally, pollutants with a lower ambient concentration (e.g., the cycloalkane and aldehyde groups) may be more subject to instrument measurement error leading to underestimation of effects.

We chose to group pollutants based on *a prior* knowledge (chemical structure) rather than the statistical relationships among them (e.g., factor analysis, principle components analysis, etc). In doing so, the group definition is not specific to the data, and will allow for replication in future studies. Collinearity could be a concern when including multiple

correlated pollutants in the same model (eq. 3 and eq. 4). One consequence of collinearity is that it could lead to inflation of the variances for individual pollutant effect estimates. However, in our approaches where multiple pollutants were included in the same model, our interest was not in estimating individual pollutant effects, but rather, the group effects. Specifically, in the random effect meta-analysis, the second stage regression accounted for this variance inflation by estimating the group effect as a weighted-average of the first stage estimates, with the inverse variance-covariance matrix of the first stage estimates serving as the weights. In the joint effect analysis, the variance of the joint effect estimate incorporates negative co-variances between individual pollutant estimates, and thus could be more modest compared to the variances of individual pollutant estimates. In addition, our relatively long time-series (over 10 years) with relatively large counts of outcome events allow for a high degree of collinearity with less impact on the estimates than would be the case for a study with fewer observations.[32]

We grouped these VOCs by chemical structure with the idea that this grouping may enhance the understanding of their health associations from commonalities that are related to their structures, such as toxicity, source, and atmospheric process. However, pollutants sharing a common chemical structure may still differ in these factors, and the estimated group effect may not be easily generalized to pollutants that fall into the same group but are not included in our analysis. For example, alkenes included in our analysis were mainly anthropogenic, as biogenic alkenes measured at Jefferson St. were lower in concentration and thus excluded from the analysis due to >10% of measurements being below detection (Supplement, eTable 1). Biogenic alkenes, such as isoprene, are important in the generation of ozone and secondary organics; these pollutants may exert health effects through pathways that are different from the anthropogenic alkenes included in this analysis.

Nonetheless, our approach allowed us to compare and understand the health associations of a large number of species in a coherent manner. Our findings further support the link between incomplete combustion and cardiovascular health, and the link between atmospheric oxidation products and respiratory health.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Sources of financial support: Research reported in this publication was supported by funding from the Electric Power Research Institute (EPRI, 10002467). This publication was also made possible by a Clean Air Research Center grant to Emory University and the Georgia Institute of Technology from the US Environmental Protection Agency (USEPA, RD834799), as well as by grants to Emory University from the USEPA (R82921301), the National Institute of Environmental Health Sciences (R01ES11294), and EPRI (EP-P27723/C13172 and EP-P4353/C2124). The content of this publication is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or the USEPA. Further, USEPA does not endorse the purchase of any commercial products or services mentioned in the publication.

The authors would like to thank the members of the Southeastern Center for Air Pollution and Epidemiology (SCAPE) research group, especially Dr. W Dana Flanders, for their thoughtful feedback. This publication is based in part upon information obtained from the Georgia Hospital Association and individual hospitals; we are grateful for the support of all participating hospitals.

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Table 1

Summary statistics of daily 24-hour average ambient air pollutants measured at the Atlanta Jefferson Street monitoring site during 8/14/1998–12/31/2008: total hydrocarbons, total oxygenates, 46 individual volatile organic compounds (VOCs) grouped by chemical structure, and four major pollutants that are included in analyses.[a]

VOC GROUPS	INDIVIDUAL VOCs	50th (25th, 75th) percentiles
	TOTALHYDROCARBONS[b]	92.7 (63.2, 159.3)
	TOTALOXYGENATES[b]	19.3 (11.8, 27.6)
HYDROCARBONS:		
N-ALKANE	Ethane	6.9 (4.9, 10.2)
	Propane[c]	**10.3 (6.5, 19.5)**
	n-Butane	6.2 (3.5, 11.0)
	n-Pentane	3.2 (2.2, 5.4)
	n-Hexane	1.5 (1.0, 2.6)
	n-Heptane	0.9 (0.6, 1.5)
	n-Octane	0.5 (0.3, 0.8)
	n-Nonane	0.6 (0.4, 0.9)
	n-Decane	0.7 (0.5, 1.3)
ISO/ANTEISO-ALKANE	i-Butane	2.3 (1.4, 4.2)
	i-Pentane[c]	**6.7 (4.3, 12.4)**
	2-Methylpentane	1.9 (1.2, 3.4)
	3-Methylpentane	1.2 (0.8, 2.1)
	2-Methylhexane	0.8 (0.5, 1.5)
	3-Methylhexane	1.1 (0.7, 1.9)
	2-Methylheptane	0.3 (0.2, 0.6)
OTHER ALKANE	2,2-Dimethylbutane	0.5 (0.3, 1.0)
	2,3-Dimethylbutane	0.6 (0.4, 1.1)
	2,3-Dimethylpentane	0.5 (0.3, 1.0)
	2,4-Dimethylpentane	0.3 (0.2, 0.7)
	2,2,4-Trimethylpentane[c]	**2.0 (1.2, 3.9)**
	2,3,4-Trimethylpentane	0.6 (0.3, 1.2)
	3-Ethylhexane	0.3 (0.2, 0.6)
CYCLOALKANE	Cyclopentane	0.3 (0.2, 0.5)
	Methylcyclopentane[c]	**0.8 (0.5, 1.4)**
	Methylcyclohexane	0.5 (0.3, 0.8)
ALKENE	**Ethylene[c]**	**3.1 (2.0, 5.4)**
	Propene	1.4 (0.9, 2.6)
ALKYNE	**Acetylene[c]**	**4.2 (2.7, 7.6)**
AROMATIC	Benzene	2.4 (1.8, 3.8)
	Toluene[c]	**7.1 (4.7, 12.5)**

VOC GROUPS	INDIVIDUAL VOCs	50th (25th, 75th) percentiles
	Ethylbenzene	1.4 (0.9, 2.4)
	n-Propylbenzene	0.4 (0.2, 0.7)
	m-Xylene & p-Xylene	3.7 (2.2, 6.9)
	o-Xylene	1.5 (0.9, 2.8)
	m-Ethyltoluene	0.6 (0.3, 1.0)
	p-Ethyltoluene	1.3 (0.8, 2.2)
	1,2,4-Trimethylbenzene[d]	1.7 (1.0, 3.0)
	1,3,5-Trimethylbenzene	0.7 (0.4, 1.2)
OXYGENATES:		
ALDEHYDE	Hexanal	0.8 (0.5, 1.1)
	Heptanal	0.6 (0.4, 0.8)
	Octanal	1.2 (0.7, 1.8)
	Decanal	0.7 (0.4, 1.1)
	Benzaldehyde[c]	**1.7 (1.2, 2.5)**
ACID	**Acetic Acid[c]**	**3.6 (1.5, 7.2)**
KETONE	**2-Butanone[c]**	**1.7 (1.0, 2.9)**
	MAJOR POLLUTANTS	**50th (25th, 75th) percentiles**
	24-hr $PM_{2.5}$ OC ($\mu g/m^3$)	3.6 (2.6, 5.0)
	1-hr max CO (ppm)	0.69 (0.43, 1.27)
	1-hr max NO_2 (ppb)	39.3 (29.5, 50.0)
	8-hr max O_3 (ppb)	39.5 (25.7, 56.7)

[a]There were 3793 days during 08/14/1998–12/31/2008. Measurements of hydrocarbons were available for 3233 of these days, while measurements of oxygenates were available for 3231 of these days. The unit is ppb-C and the limit of detection (LOD) is 0.1 ppb-C for all VOCs. VOC concentrations below 0.1 ppb-C were replaced with 0.05 ppb-C in all analyses.

[b]Total hydrocarbons denotes total identified non-methane hydrocarbons. Total oxygenates denotes total identified oxygenated hydrocarbons.

[c]Species in bold text are the indicator pollutants for each VOC group.

[d]1,2,4-Trimethylbenzene & sec-Butylbenzene

Table 2

Estimated associations between VOC groups and cardiovascular and asthma emergency department (ED) visits using three analytic approaches.[a]

VOC GROUPS	INDICATOR POLLUTANT APPROACH[b]	JOINT EFFECT ANALYSIS[c]	RANDOM EFFECT META-ANALYSIS[d]
	CARDIOVASCULAR ED VISITS AMONG ALL AGES		
HYDROCARBONS			
N-ALKANE	1.002 (1.000, 1.005)	1.006 (1.001, 1.011)	0.999 (0.997, 1.001)
ISO/ANTEISO-ALKANE	1.004 (1.001, 1.008)	1.005 (1.000, 1.010)	1.000 (0.997, 1.003)
OTHER ALKANE	1.005 (1.001, 1.008)	1.006 (1.001, 1.011)	1.000 (0.997, 1.002)
CYCLOALKANE	1.005 (1.001, 1.009)	1.005 (1.001, 1.010)	1.002 (0.997, 1.007)
ALKENE	1.006 (1.002, 1.009)	1.006 (1.002, 1.009)	1.001 (0.997, 1.006)
ALKYNE	1.006 (1.003, 1.010)	1.006 (1.003, 1.010)	1.007 (1.001, 1.012)
AROMATIC	1.006 (1.002, 1.010)	0.998 (0.992, 1.005)	1.000 (0.999, 1.001)
OXYGENATES			
ALDEHYDE	1.001 (0.998, 1.004)	1.008 (1.000, 1.016)	1.000 (0.998, 1.002)
ACID	1.002 (0.995, 1.010)	1.002 (0.995, 1.010)	1.001 (0.993, 1.009)
KETONE	1.005 (0.995, 1.014)	1.005 (0.995, 1.014)	1.003 (0.993, 1.013)
	ASTHMA ED VISITS AMONG ALL AGES		
HYDROCARBONS			
N-ALKANE	1.004 (1.000, 1.009)	1.005 (0.995, 1.014)	0.999 (0.994, 1.003)
ISO/ANTEISO-ALKANE	1.006 (1.000, 1.013)	1.010 (1.000, 1.019)	1.006 (0.999, 1.013)
OTHER ALKANE	1.006 (1.000, 1.013)	1.007 (0.999, 1.016)	0.999 (0.993, 1.004)
CYCLOALKANE	1.009 (1.002, 1.016)	1.009 (1.002, 1.016)	0.995 (0.986, 1.007)
ALKENE	1.005 (0.998, 1.011)	1.005 (0.998, 1.011)	0.992 (0.983, 1.003)
ALKYNE	1.006 (0.999, 1.012)	1.006 (0.999, 1.012)	1.000 (0.987, 1.014)
AROMATIC	1.009 (1.002, 1.017)	1.008 (0.995, 1.021)	1.002 (0.998, 1.005)
OXYGENATES			
ALDEHYDE	0.998 (0.991, 1.005)	1.021 (1.004, 1.037)	1.000 (0.995, 1.006)
ACID	1.008 (0.991, 1.026)	1.008 (0.991, 1.026)	1.003 (0.983, 1.021)
KETONE	1.026 (1.004, 1.048)	1.026 (1.004, 1.048)	1.024 (1.000, 1.049)

[a]This analysis included 3224 days on which all VOCs were available during 8/14/1998–12/31/2008. VOC concentrations below the limit of detection (LOD) of 0.1 ppb-C were replaced with 0.05 ppb-C in all analyses. We used same-day (lag 0) pollution levels in models predicting cardiovascular ED visits and 3-day moving average (of lags 0, 1, and 2) pollution levels in models predicting asthma ED visits. All methods included the same covariate control for temporal trends and meteorology: time splines with monthly knots, cubic function of same-day maximum temperature, cubic function of lag 1–2-day moving average minimum temperature (when using 3-day moving average pollution levels), cubic function of mean dew point temperature (same-day or 3-day moving average, matching the temporal metric of the pollution term), day of week, indicators for holidays, seasons, season-maximum temperature interaction, season-day of week interaction, and indicators for hospital participation periods. The estimated associations are expressed as rate ratios (95% confidence interval) per interquartile range (IQR) increase in pollutant concentrations (listed in Table 1).

[b]The "indicator pollutant approach" estimated the effect of each indicator pollutant increasing by its IQR in single-pollutant models.

[c]The "joint effect analysis" estimated the effect of all pollutants in a group jointly increasing by their IQRs in multi-pollutant models that included all pollutants of the group. The joint effect estimates for VOC groups comprised of only one pollutant were the same as the estimates obtained from the indicator pollutant approach.

[d]The "random effect meta-analysis" estimated the mean effect of any of the pollutants in a group increasing by its IQR in a two-stage regression, where the 46 individual pollutant effects were estimated simultaneously in the Poisson model in the first stage, and the mean of each group was estimated under a Bayesian framework using Markov chain Monte Carlo in the second stage. The estimated rate ratio (95% CI) for the random effect meta-analysis is median (2.5^{th}, 97.5^{th} percentiles) from the posterior distribution.

Table 3

Sensitivity analyses evaluating model misspecification and confounding by VOCs.[a]

VOC GROUPS	PRIMARY ANALYSIS[b]	LAG NEGATIVE 1 [c]	CONTROL FOR OTHER VOC GROUPS[d]
CARDIOVASCULAR ED VISITS AMONG ALL AGES			
HYDROCARBONS			
N-ALKANE	1.002 (1.000, 1.005)	1.002 (0.999, 1.005)	1.000 (0.997, 1.003)
ISO/ANTEISO-ALKANE	1.004 (1.001, 1.008)	1.003 (0.999, 1.007)	0.996 (0.985, 1.008)
OTHER ALKANE	1.005 (1.001, 1.008)	1.002 (0.998, 1.006)	0.994 (0.981, 1.007)
CYCLOALKANE	1.005 (1.001, 1.009)	1.003 (0.999, 1.007)	1.002 (0.988, 1.016)
ALKENE	1.006 (1.002, 1.009)	1.002 (0.998, 1.005)	1.005 (0.998, 1.011)
ALKYNE	1.006 (1.003, 1.010)	1.002 (0.998, 1.006)	1.005 (1.000, 1.011)
AROMATIC	1.006 (1.002, 1.010)	1.002 (0.997, 1.006)	1.005 (0.988, 1.021)
OXYGENATES			
ALDEHYDE	1.001 (0.998, 1.004)	0.999 (0.996, 1.002)	1.000 (0.997, 1.003)
ACID	1.002 (0.995, 1.010)	1.010 (1.002, 1.018)	1.001 (0.993, 1.009)
KETONE	1.005 (0.995, 1.014)	1.012 (1.002, 1.021)	1.003 (0.993, 1.013)
ASTHMA ED VISITS AMONG ALL AGES			
HYDROCARBONS			
N-ALKANE	1.004 (1.000, 1.009)	1.000 (0.997, 1.003)	1.001 (0.995, 1.007)
ISO/ANTEISO-ALKANE	1.006 (1.000, 1.013)	1.000 (0.996, 1.005)	0.986 (0.963, 1.010)
OTHER ALKANE	1.006 (1.000, 1.013)	1.002 (0.998, 1.007)	0.985 (0.961, 1.009)
CYCLOALKANE	1.009 (1.002, 1.016)	1.001 (0.996, 1.006)	1.027 (0.999, 1.056)
ALKENE	1.005 (0.998, 1.011)	1.002 (0.998, 1.007)	0.993 (0.979, 1.006)
ALKYNE	1.006 (0.999, 1.012)	1.004 (1.000, 1.008)	1.001 (0.990, 1.013)
AROMATIC	1.009 (1.002, 1.017)	1.002 (0.997, 1.007)	1.019 (0.987, 1.052)
OXYGENATES			
ALDEHYDE	0.998 (0.991, 1.005)	1.002 (0.998, 1.006)	0.994 (0.987, 1.001)
ACID	1.008 (0.991, 1.026)	0.998 (0.987, 1.010)	1.001 (0.984, 1.020)
KETONE	1.026 (1.004, 1.048)	1.003 (0.990, 1.017)	1.027 (1.003, 1.050)

VOC indicates volatile organic compounds, LOD limit of detection, ED emergency department.

[a]These analyses included 3224 days on which all VOCs were available during 8/14/1998–12/31/2008. VOC concentrations below the limit of detection (LOD) of 0.1 ppb-C were replaced with 0.05 ppb-C in all analyses. We used same-day (lag 0) pollution levels in models predicting cardiovascular ED visits and 3-day moving average (of lags 0, 1, and 2) pollution levels in models predicting asthma ED visits. All methods included the same covariate control for temporal trends and meteorology: time splines with monthly knots, cubic function of same-day maximum temperature, cubic function of lag 1–2-day moving average minimum temperature (when using 3-day moving average pollution levels), cubic function of mean dew point temperature (same-day or 3-day moving average, matching the temporal metric of the pollution term), day of week, indicators for holidays, seasons, season-maximum temperature interaction, season-day of week interaction, and indicators for hospital participation periods. The estimated associations are expressed as rate ratios (95% confidence interval) per interquartile range (IQR) increase in pollutant concentrations (listed in Table 1).

[b]The "primary analysis" is the indicator pollutant approach in the primary analysis. It estimated the effect of each indicator pollutant increasing by its IQR in single-pollutant models.

[c]The "lag negative 1" is based on indicator pollutant approach. It estimated the associations between tomorrow's indicator pollutant level (lag negative 1) and today's ED visits, controlling for today's indicator pollutant and covariate levels. We reported the estimates of the lag negative 1 pollutant levels in this column.

[d]The "control for other VOC groups" included all indicator pollutants in one model simultaneously.

Table 4

Sensitivity analysis controlling for selected major pollutants one at a time in each VOC indicator pollutant model predicting cardiovascular ED visits among all ages.[a]

		$PM_{2.5}$ OC	CO	NO2	O3
SINGLE-POLLUTANT MODELS OF MAJOR POLLUTANTS: →		1.006 (1.000, 1.012)	1.009 (1.003, 1.015)	1.004 (0.995, 1.013)	1.001 (0.985, 1.017)
SINGLE-POLLUTANT MODELS OF VOC INDICATOR POLLUTANTS: ↓		**TWO-POLLUTANT MODELS: MAJOR POLLUTANT (TOP OF CELL). VOC INDICATOR POLLUTANT (BOTTOM OF CELL).**			
		1.006 (0.999, 1.012)	1.009 (1.003, 1.016)	1.003 (0.994, 1.013)	1.001 (0.984, 1.017)
N-ALKANE	1.001 (0.999, 1.004)	1.001 (0.998, 1.003)	1.000 (0.997, 1.003)	1.001 (0.998, 1.004)	1.001 (0.999, 1.004)
		1.005 (0.998, 1.012)	1.011 (1.003, 1.019)	1.002 (0.993, 1.012)	1.000 (0.984, 1.017)
ISO/ANTEISO-ALKANE	1.003 (0.999, 1.007)	1.001 (0.996, 1.006)	0.998 (0.993, 1.004)	1.002 (0.998, 1.007)	1.003 (0.999, 1.007)
		1.005 (0.998, 1.012)	1.011 (1.003, 1.019)	1.002 (0.993, 1.012)	1.000 (0.984, 1.017)
OTHER ALKANE	1.003 (0.999, 1.007)	1.001 (0.996, 1.006)	0.998 (0.992, 1.004)	1.003 (0.998, 1.007)	1.003 (0.999, 1.007)
		1.004 (0.997, 1.012)	1.010 (1.002, 1.018)	1.002 (0.992, 1.011)	1.000 (0.984, 1.017)
CYCLOALKANE	1.004 (0.999, 1.008)	1.002 (0.997, 1.007)	0.999 (0.994, 1.005)	1.004 (0999, 1.008)	1.004 (0.999, 1.008)
		1.001 (0.994, 1.009)	1.006 (0.998, 1.014)	1.000 (0.991, 1.010)	1.001 (0.985, 1.017)
ALKENE	1.006 (1.002, 1.010)	1.005 (1.001, 1.010)	1.003 (0.998, 1.008)	1.006 (1.002, 1.010)	1.006 (1.002, 1.010)
		1.002 (0.995, 1.010)	1.007 (0.999, 1.014)	1.001 (0.992, 1.010)	1.001 (0.985, 1.017)
ALKYNE	1.005 (1.001, 1.008)	1.004 (1.000, 1.008)	1.002 (0.998, 1.007)	1.005 (1.001, 1.008)	1.005 (1.001, 1.008)
		1.004 (0.996, 1.011)	1.009 (1.001, 1.018)	1.001 (0.992, 1.011)	1.000 (0.984, 1.017)
AROMATIC	1.005 (1.000, 1.009)	1.003 (0.998, 1.009)	1.000 (0.994, 1.006)	1.004 (0.999, 1.009)	1.005 (1.000, 1.009)
		1.006 (1.000, 1.012)	1.009 (1.003, 1.015)	1.004 (0.995, 1.013)	1.001 (0.985, 1.017)
ALDEHYDE	1.000 (0.991, 1.008)	1.000 (0.997, 1.003)	1.000 (0.997, 1.003)	1.000 (0.997, 1.003)	1.000 (0.997, 1.003)
		1.006 (1.000, 1.012)	1.009 (1.003, 1.015)	1.004 (0.995, 1.013)	1.001 (0.985, 1.017)
ACID	1.000 (0.991, 1.008)	0.999 (0.991, 1.008)	0.999 (0.991, 1.008)	1.000 (0.991, 1.008)	1.000 (0.991, 1.008)
		1.006 (0.999, 1.012)	1.009 (1.003, 1.015)	1.004 (0.995, 1.013)	1.001 (0.985, 1.017)
KETONE	1.006 (0.996, 1.016)	1.005 (0.995, 1.015)	1.005 (0.995, 1.015)	1.005 (0.996, 1.015)	1.006 (0.996, 1.016)

[a]This analysis included 2997 days during 8/14/1998–12/31/2008 for which both data on major pollutants and VOCs were available. VOC concentrations below the limit of detection (LOD) of 0.1 ppb-C were replaced with 0.05 ppb-C in all analyses. We used same-day (lag 0) pollution levels in models predicting cardiovascular ED visits. All methods included the same covariate control for temporal trends and meteorology: time splines with monthly knots, cubic function of same-day maximum temperature, cubic function of mean dew point temperature (lag 0), day of week, indicators for holidays, seasons,

season-maximum temperature interaction, season-day of week interaction, and indicators for hospital participation periods. The estimated associations are expressed as rate ratios (95% confidence interval) per interquartile range (IQR) increase in pollutant concentrations (listed in Table 1).

Table 5

Sensitivity analysis controlling for selected major pollutants one at a time in each VOC indicator pollutant model predicting asthma ED visits among all ages.[a]

		$PM_{2.5}$ OC	CO	NO2	O3
SINGLE-POLLUTANT MODELS OF MAJOR POLLUTANTS: →		1.019 (1.007, 1.030)	1.018 (1.007, 1.030)	1.031 (1.014, 1.049)	1.037 (1.009, 1.066)
SINGLE-POLLUTANT MODELS OF VOC INDICATOR POLLUTANTS: ↓		**TWO-POLLUTANT MODELS: MAJOR POLLUTANT (TOP OF CELL). VOC INDICATOR POLLUTANT (BOTTOM OF CELL).**			
		1.015 (1.002, 1.028)	1.015 (1.001, 1.029)	1.027 (1.009, 1.046)	1.033 (1.004, 1.062)
N-ALKANE	1.006 (1.001,1.011)	1.003 (0.998, 1.009)	1.003 (0.997, 1.009)	1.004 (0.998, 1.009)	1.005 (1.000, 1.010)
		1.012 (0.997, 1.028)	1.012 (0.994, 1.030)	1.024 (1.005, 1.044)	1.030 (1.001, 1.059)
ISO/ANTEISO-ALKANE	1.012 (1.004, 1.020)	1.007 (0.996, 1.017)	1.006 (0.994, 1.018)	1.007 (0.998, 1.016)	1.010 (1.002, 1.018)
		1.014 (0.999, 1.030)	1.015 (0.997, 1.034)	1.026 (1.007, 1.046)	1.030 (1.002, 1.060)
OTHER ALKANE	1.011 (1.003, 1.020)	1.005 (0.994, 1.016)	1.003 (0.990, 1.016)	1.006 (0.997, 1.015)	1.010 (1.001, 1.018)
		1.010 (0.994, 1.025)	1.008 (0.990, 1.026)	1.023 (1.003, 1.042)	1.029 (1.001, 1.058)
CYCLOALKANE	1.014 (1.006, 1.022)	1.009 (0.999, 1.020)	1.009 (0.997, 1.022)	1.009 (1.000, 1.018)	1.012 (1.004, 1.021)
		1.019 (1.003, 1.034)	1.021 (1.004, 1.039)	1.029 (1.010, 1.048)	1.034 (1.005, 1.063)
ALKENE	1.008 (1.000, 1.015)	1.000 (0.990, 1.010)	0.998 (0.987, 1.009)	1.003 (0.995, 1.011)	1.007 (0.999, 1.014)
		1.015 (1.001, 1.030)	1.017 (1.000, 1.035)	1.027 (1.008, 1.046)	1.033 (1.005, 1.063)
ALKYNE	1.009 (1.002, 1.016)	1.003 (0.994, 1.012)	1.001 (0.990, 1.012)	1.005 (0.997, 1.012)	1.008 (1.001, 1.015)
		1.012 (0.996, 1.028)	1.012 (0.994, 1.031)	1.024 (1.005, 1.044)	1.030 (1.002, 1.059)
AROMATIC	1.013 (1.004, 1.022)	1.007 (0.995, 1.019)	1.006 (0.992, 1.020)	1.007 (0.998, 1.017)	1.011 (1.003, 1.020)
		1.019 (1.007, 1.032)	1.019 (1.007, 1.031)	1.032 (1.014, 1.050)	1.037 (1.009, 1.066)
ALDEHYDE	1.000 (0.993, 1.007)	0.997 (0.990, 1.004)	0.998 (0.991, 1.005)	0.998 (0.991, 1.005)	0.999 (0.992, 1.006)
		1.018 (1.006, 1.030)	1.018 (1.006, 1.030)	1.031 (1.013, 1.049)	1.036 (1.007, 1.065)
ACID	1.011 (0.990, 1.032)	1.009 (0.989, 1.030)	1.009 (0.988, 1.030)	1.008 (0.988, 1.029)	1.008 (0.987, 1.029)
		1.017 (1.005, 1.029)	1.017 (1.005, 1.028)	1.029 (1.011, 1.047)	1.033 (1.004, 1.062)
KETONE	1.030 (1.007, 1.054)	1.025 (1.001, 1.049)	1.025 (1.001, 1.050)	1.025 (1.001, 1.049)	1.027 (1.003, 1.051)

[a]This analysis included 2997 days during 8/14/1998–12/31/2008 for which both data on major pollutants and VOCs were available. VOC concentrations below the limit of detection (LOD) of 0.1 ppb-C were replaced with 0.05 ppb-C in all analyses. We used 3-day moving average (of lags 0, 1, and 2) pollution levels in models predicting asthma ED visits. All methods included the same covariate control for temporal trends and meteorology: time splines with monthly knots, cubic function of same-day maximum temperature, cubic function of lag 1–2-day moving average minimum temperature, cubic function of mean dew point temperature (3-day moving average), day of week, indicators for holidays, seasons, season-maximum temperature interaction, season-day of week interaction, and indicators for hospital participation periods. The estimated associations are expressed as rate ratios (95% confidence interval) per interquartile range (IQR) increase in pollutant concentrations (listed in Table 1).