EVALUATION OF HEALTH EFFECTS OF TOXIC AIR POLLUTANTS IN A SOUTHERN CALIFORNIA COMMUNITY: A PILOT STUDY

Funded by the California Air Resources Board & South Coast Air Quality Management District

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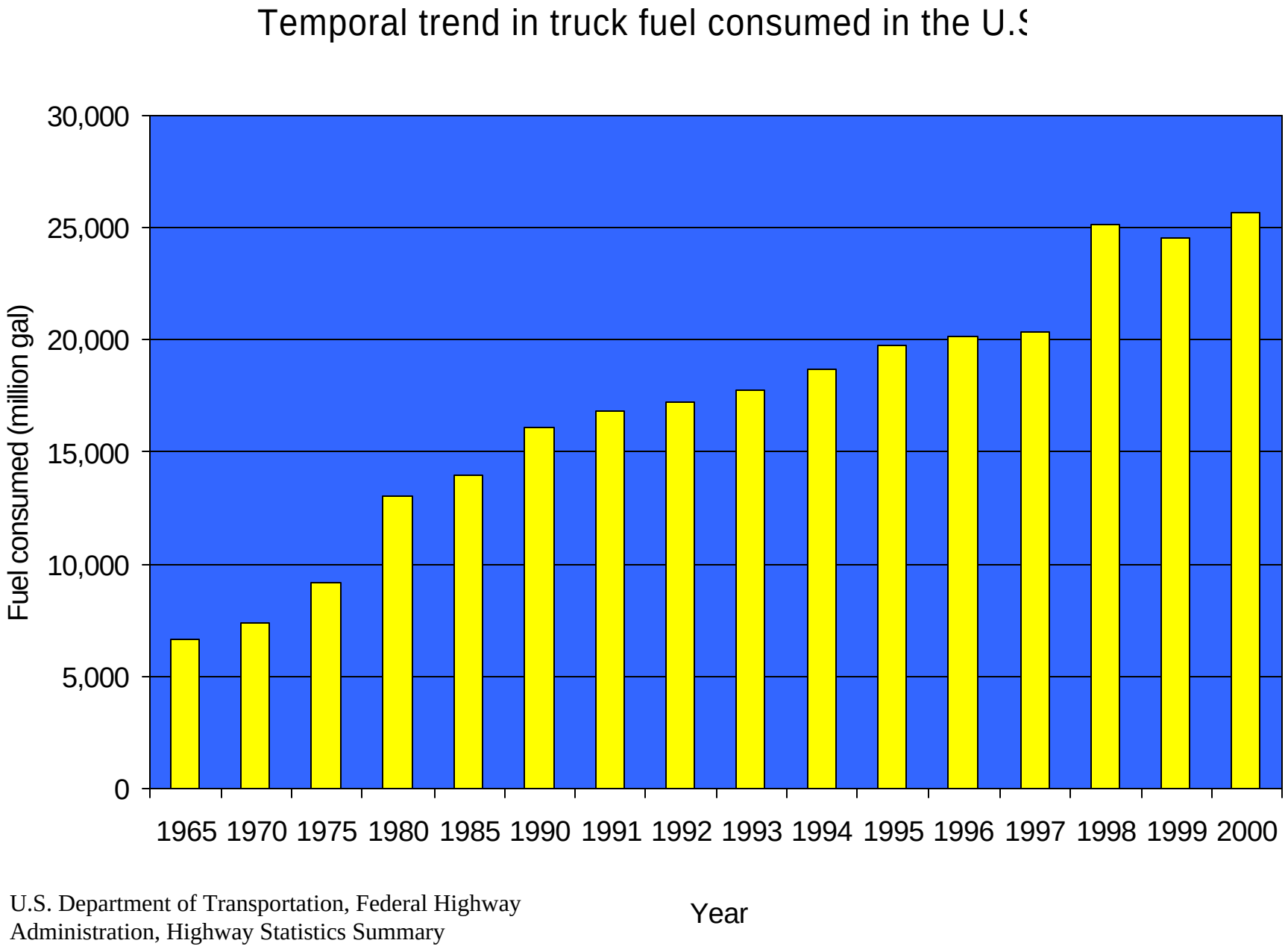
Research Objectives

- to examine the relationship of acute asthma in children to concentrations of volatile organic compounds (VOCs) measured in exhaled breath samples and at an outdoor ambient site.

- to conduct an exposure assessment study to estimate the statistical associations between breath, ambient, personal and indoor concentrations of VOCs.

Importance

- Knowledge base on non-cancer effects of urban air toxics is limited.
- Asthma morbidity has steadily increased since the mid-1970's;
- Regulated criteria air pollutants (e.g., ozone) have decreased;
- Indoor air toxics and some outdoor traffic-related air toxics may have increased;



U.S. Department of Transportation, Federal Highway Administration, Highway Statistics Summary

Definition of Toxic Air Pollutants

"air toxics" or "hazardous air pollutants"

- have the potential to cause serious adverse health effects in the general population or organisms in the environment as a result of ambient exposures;
- are released from anthropogenic sources;
- do not include principal criteria air pollutants: PM_{10}, $PM_{2.5}$, O_3, NO_2, CO, SO_2
  (sections 108-110 Clean Air Act);
- do include 188 hazardous air pollutants
  (section 112.b.1, Clean Air Act).

Adapted from: Patrick, DR. Toxic Air Pollution Handbook. 1994

Asthma Phenotype

- Intermittent and reversible airway obstruction;
- Airway hyperresponsiveness to contractile stimuli;
- Airway inflammation: infiltration of inflammatory cells releasing cytokines, chemokines & chemical mediators.

Inflammation in Asthma

- IgE-mediated inflammation;
- Neurogenic or Irritant-induced inflammation;
- Reactive airways dysfunction syndrome (RADS): irritant-induced non-immunological asthma with no latency period.

Heterogeneity of Asthma

- Age at onset: pediatric vs. adult,
  occupational factors are occasionally relevant to adult onset asthma, early childhood exposures to allergens & LRI for pediatric asthma;
- Importance of atopy:
  allergic & non-allergic asthma -- both show similar profiles of inflammatory mediators;
- Specific inducers of acute asthma:
  allergenic, largely high molecular weight (e.g., fungal or animal proteins) acting by IgE-mediated mechanisms &
  non-allergenic, largely low molecular weight, may act as haptens (e.g., diisocyanates) or irritants (e.g., ozone);
- Severity and Response to treatment.

Overview of Asthma and Air Toxics Research

- Epidemiologic studies are largely limited to effects of "criteria air pollutants" (PM_{10}, $PM_{2.5}$, O_3, NO_2, CO, SO_2) & some PM fractions (e.g., sulfate)
- Experimental research on toxic compounds is largely limited to animal data;
- Occupational literature has some "fortuitous" data on high exposures, but results have limited relevance to community exposures by susceptible people.

Traffic-Related Air Pollution, Asthma & Allergy

- Cross-sectional study of 3,133 Japanese: Prevalence of cedar pollen allergy increased near busy highways despite equivalent local exposure to cedar pollen.
  Ishizaki et al. *Annals of Allergy*, 1987 Apr, 58(4):265-70.

- Clinical cross-over study of 20 mild allergic asthmatics: Early & late-phase bronchospastic reactions to allergen challenge were greater following 30-min road tunnel exposure (NO_2 > 159 ppb, $PM_{2.5}$ >100 μg/m^3) vs control exposure.
  Svartengren et al. *Euro Respir J*, 2000 15:716-24.

Traffic-Related Air Pollution, Asthma & Allergy

- Panel study of 61 children in summer (77% on asthma med's):
  Stronger associations were found for black smoke than for PM_{10}, in relation to PEF, respiratory symptoms and bronchodilator use.
  Gielen et al. *Am J Respir Crit Care Med*. 1997; 155:2105-2108.

- Black smoke / 12 schools in Netherlands significantly correlated with NO_2 ($r = 0.74$) & truck traffic density ($r = 0.67$), but not PM_{10} ($r < 0.3$).

  Roorda-Knape. Atmos Environ, 1998; 32:1921-30

Traffic-Related Air Pollution, Asthma & Allergy

- Numerous epidemiologic studies have shown associations between traffic density and asthma prevalence or morbidity.

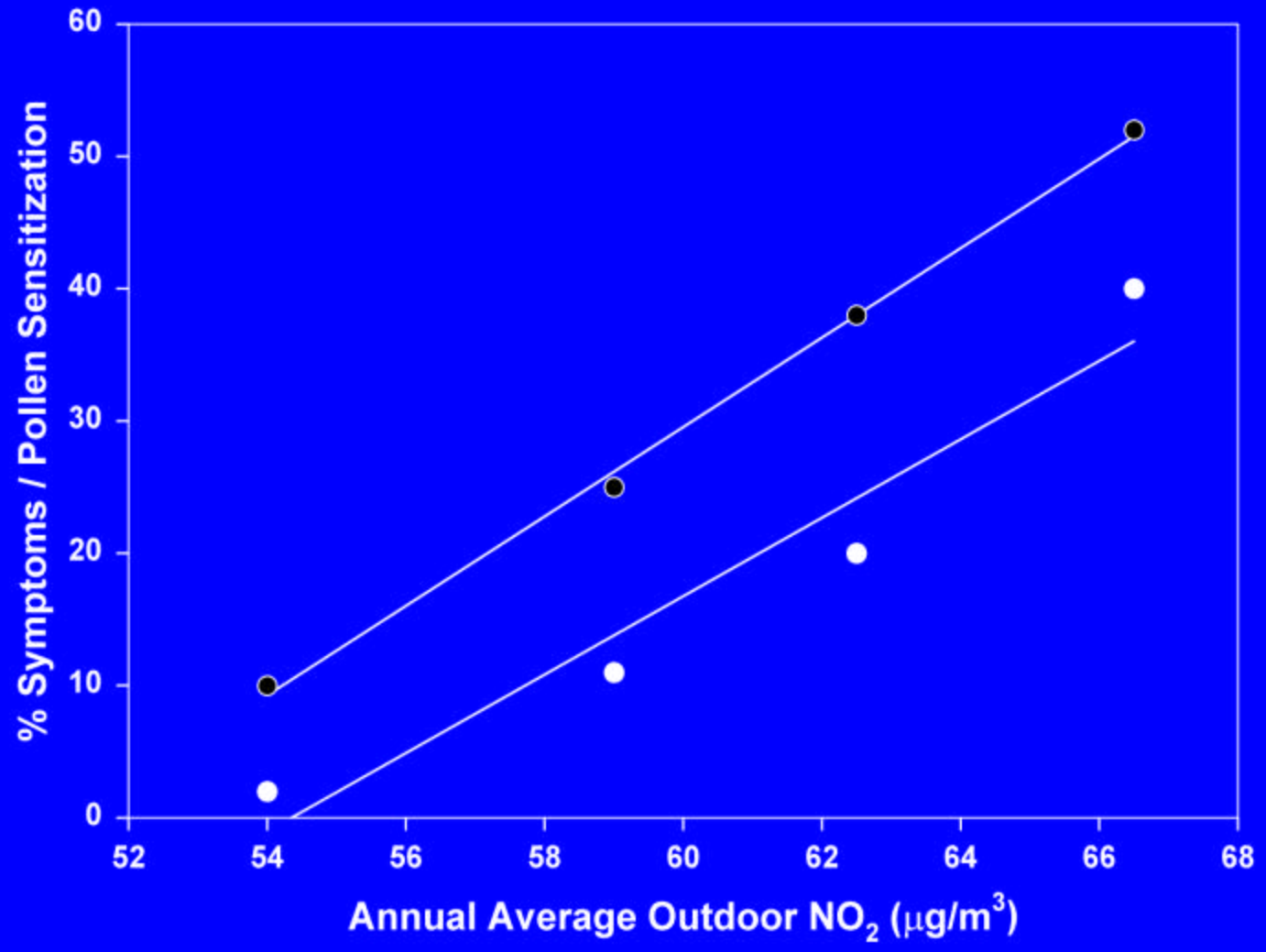
- Study of 317 children living near major roads; NO_2 personal samplers, outdoor home samplers:

  • Outdoor NO_2 predicted traffic density, not personal NO_2.

  • Atopic sensitization (pollen, HDM/cat, milk/egg), Dx hay fever, and reported symptoms of allergic rhinitis and wheezing were associated with urban outdoor NO_2 but not personal NO_2

Krämer et al. *Epidemiol*, 2000; 11(1):64-70.

Relationship between outdoor home NO_2 near busy streets to pollen sensitization and to symptoms of allergic rhinitis in 202 children, 9 years of age, Dusseltal and Friedrichstadt, Germany.



Did outdoor NO_2 from traffic act as a surrogate for PAH and other air toxics exposures?

Significant contribution of traffic-related PAH to indoor PAH was detected with real-time monitoring methods, adjusting for indoor sources at 3 non-smoking indoor sites with different traffic densities:

Indoor peaks occur during morning rush hour, on weekdays only max = 65 ng/m^3 for the most urban location

Geo. mean urban:	31 ng/m^3
Geo. mean semi-urban:	19 ng/m^3
Geo. mean suburban:	8 ng/m^3

Dubowsky, et al. *J Expo Anal Environ Epidemiol*, 1999; 9:312-21.

Summary of Experimental Data on PAH

see Nel et al., *Curr Opin Pulm Med*. 2001;7:20-6.

- PAH from fossil fuel combustion (DEP) may contribute to:
  - worsening respiratory allergic responses (enhanced IgE & cytokine responses to allergen challenge)
  - induction of the initial clinical expression (allergic sensitization to neoantigens)
- Clinical relevance remains to be established.
- Relevance to epidemiologic findings & to public health remains to be established

Formaldehyde, Asthma and Atopy in Children

- 62 8 y/o children -- both formaldehyde levels and specific IgE to formaldehyde were higher in particleboard vs brick classes. IgE and formaldehyde decreased significantly after transfer to brick school.
  Wantke et al. *Clin Experimental Allergy*, 1996; 26:276-80.

- 148 children (53 asthmatic) --increased risk of allergic sensitization to common allergens:
  per 10 $\mu g/m^3$ formaldehyde, OR 1.40 (0.98-2.00).
  Also found possible increased risk for asthma & symptoms.
  Garrett et al. Allergy, 1999 Apr, 54(4):330-7.

Formaldehyde, Asthma and Atopy in Children

- 224 healthy children -- significant increase in exhaled NO in children with mean home formaldehyde ≥ 40 μg/m^3.
  Franklin et al. *Am J Respir Crit Care Med*, 2000; 161:1757-9.

- 298 children -- increased prevalence of asthma & chronic bronchitis / homes with 48-96 μg/m^3 vs lower formaldehyde conc.;
  22% decrease in PEF per 48 μg/m^3.
  Krzyzanowski et al, Environ Res, 1990, 52:117-25.

VOC Mixtures and Asthma: Clinical Studies

- 11 asthmatics with His hyperreactivity. Clean air, and VOC mixtures at 2.5 & 25 mg/m^3: no change in FEV_1 or histamine reactivity

  Harving et al., *Am Rev Respir Dis*, 1991; 143:751-4.

- 14 healthy nonsmoking young adult men. Clean air and 25 mg/m^3 of a VOC mixture. Nasal lavage immediately after exposure and 18 h later showed significant increases in neutrophils.

  Koren HS, et al. Arch Environ Health 47:39-44 (1992).

VOC Mixtures & Asthma: Epidemiologic Studies

- Survey 627 students 13-14 y/o, 11 schools Uppsala, Sweden.

  Self-reported asthma prevalence (N=40) was higher in schools with higher VOCs (passive not active). No indoor allergen data.

  Smedje et al. *Clin Experimental Allergy*, 1997; 27:1270-8.

VOC Mixtures & Asthma: Epidemiologic Studies

- Survey of adults 20-44 y/o in Uppsala, Sweden, nonrandom subsample of 47 with asthma symptoms, random subsample of 41 with no symptoms.

  Findings for 2-hr active VOC samples in homes:
  - Nocturnal breathlessness:
    associated with Toluene, C8-aromatics, Terpenes & formaldehyde in adjusted LR models;
  - Bronchial hyperresponsiveness was only correlated with limonene;
  - PEF variability was only correlated with terpenes.

Norbäck et al., *Occup Environ Med* 1995; 52:388-95.

VOC Mixtures and Asthma: The Kanawha County Health Study

- Large chemical manufacturing center, WV;
- 74 elementary schools -- 8,549 children studied in and out of valley – higher VOC concentrations in the valley;
- Passive 8-wk samples of 5 petroleum-related and 10 process-related compounds;

Ware JH, et al. Am J Epidemiol 137:1287-301 (1993).

Results: Kanawha County Health Study

- Cross-sectional findings: children in the valley had higher rates of MD-Dx asthma:
  OR 1.27 (95% CI 1.09, 1.48);
- Chronic lower respiratory symptoms and asthma Dx were weakly positively associated with VOCs;
- One school with high petroleum-related VOCs strongly influenced the model.

Comparison of Kanawha Valley to the South Coast Air Basin of Southern California and in-car VOCs

Compound	Kanawha Study (mean)	SCAQMD MATES II (mean)	In Cars, NY City (range)*
Toluene ($\mu g/m^3$)	9.7	13.0	26-56
Benzene ($\mu g/m^3$)	3.2	3.5	9-11

* Wixtrom & Brown. *J Exp Anal Environ Epidemiol*, 1992; 2:23-78.
Weisel et al. *J Exp Anal Environ Epidemiol*, 1992; 2:79-96

Epidemiologic time series

- Associations between ER visits for asthma by children and ambient benzene in Belfast. Smaller associations for criteria air pollutants (PM_{10}, NO_2, SO_2 and CO). Benzene association was more robust than PM_{10} in a 2-pollutant model.

  Thompson et al. *Arch Environ Health*. 2001;56:234-41.

- Benzene, toluene, 1,3-butadiene, ethylbenzene, *m*,*p*-xylene, and *o*-xylene were associated with emergency room visits for symptoms of acute wheeze in children < 2 yrs. Similar associations for criteria pollutants (PM_{10}, NO_2, SO_2) but less significant.

  Buchdahl et al. *Occup Environ Med*. 2000;57:86-93.

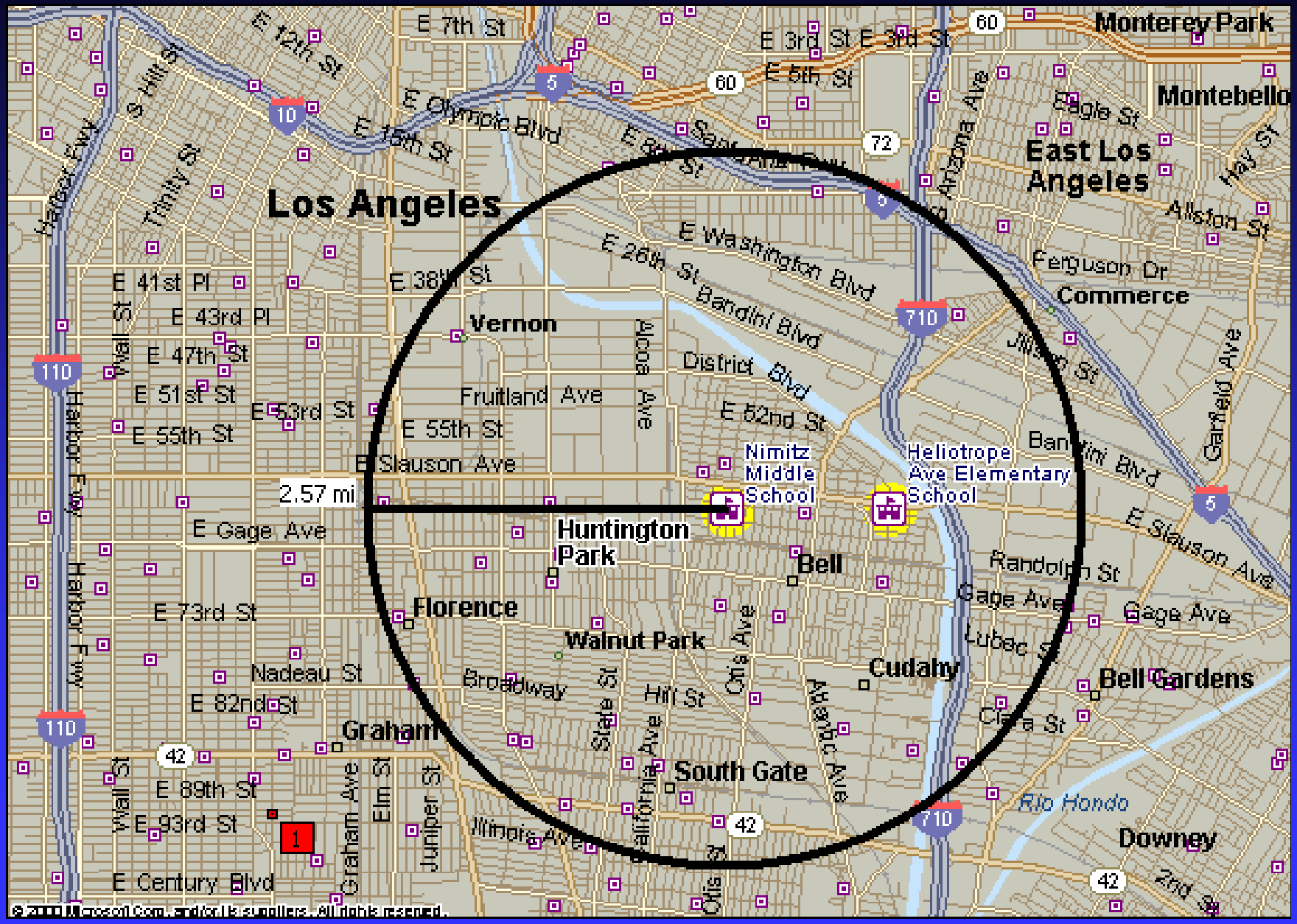
Study Design

- Asthma panel study.
- Definition:
  a longitudinal study with repeated measurements of health outcomes and exposures in individuals, taken over equally spaced periods.
- Daily repeated health outcomes 35-84 days per child, Nov 1999 to Jan 2000.

Study region

- Huntington Park, among the highest VOC concentrations in CARB MATES II study.
- Low SES Hispanic community *flanked by 4 freeways - 5, 10, 110, 710.*
- Local trucking routes
- Light industry

Figure 1. Huntington Park Region Study Map.



Eligibility Criteria

- minimum 1-yr history MD-diagnosed asthma
- age 10-15
- nonsmokers who live in nonsmoking households
- home and school addresses within a 3-mile radius of the central air monitoring site
- Persistent asthma symptoms (2 or more/wk), relaxed to intermittent asthma few times/mo.

Asthma Symptoms

- Subjects reported symptoms on an ordinal scale 0-5:
  relevant to impact of asthma on daily life.
- Dichotomized for analysis to model risk of symptoms that were bothersome or interfered with daily activities (score 2 or greater).

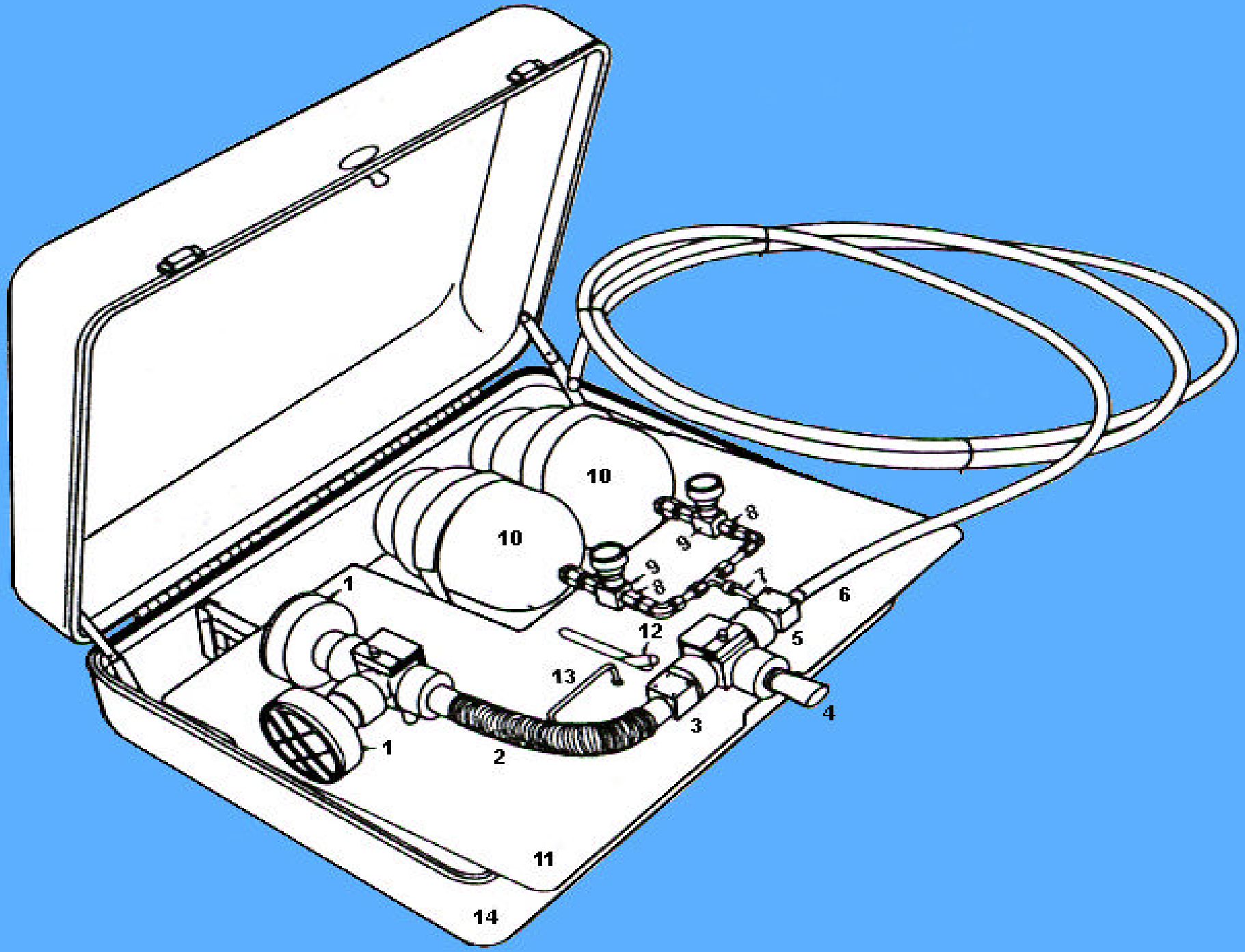
Subject Characteristics

No. males / No. females	18 / 4
Median age (age Range)	12 (10-16) years
No. days with bothersome or more severe asthma symptoms	79 / 1,123 person-days (7.0%)
No. with % predicted $FEV_1 < 80\%$	14 (64%)
No. on anti-inflammatory medications	6 (27%)
Mean daily as-needed β-agonist inhaler puffs (SD)	1.32 (1.79)

Exposure Measurements

- 141 Summa breath canisters collected for VOCs: Benzene; Carbon tetrachloride; Chloroform; Methylene Chloride; 1,1-Dichloroethane; *o*-Dichlorobenzene; *p*-Dichlorobenzene Styrene; Tetrachloroethylene; Toluene; *m*,*p*-Xylene; *o*-Xylene;.

- Subjects instructed to give breath samples during asthma exacerbations and at baseline periods free of asthma at least 3 days.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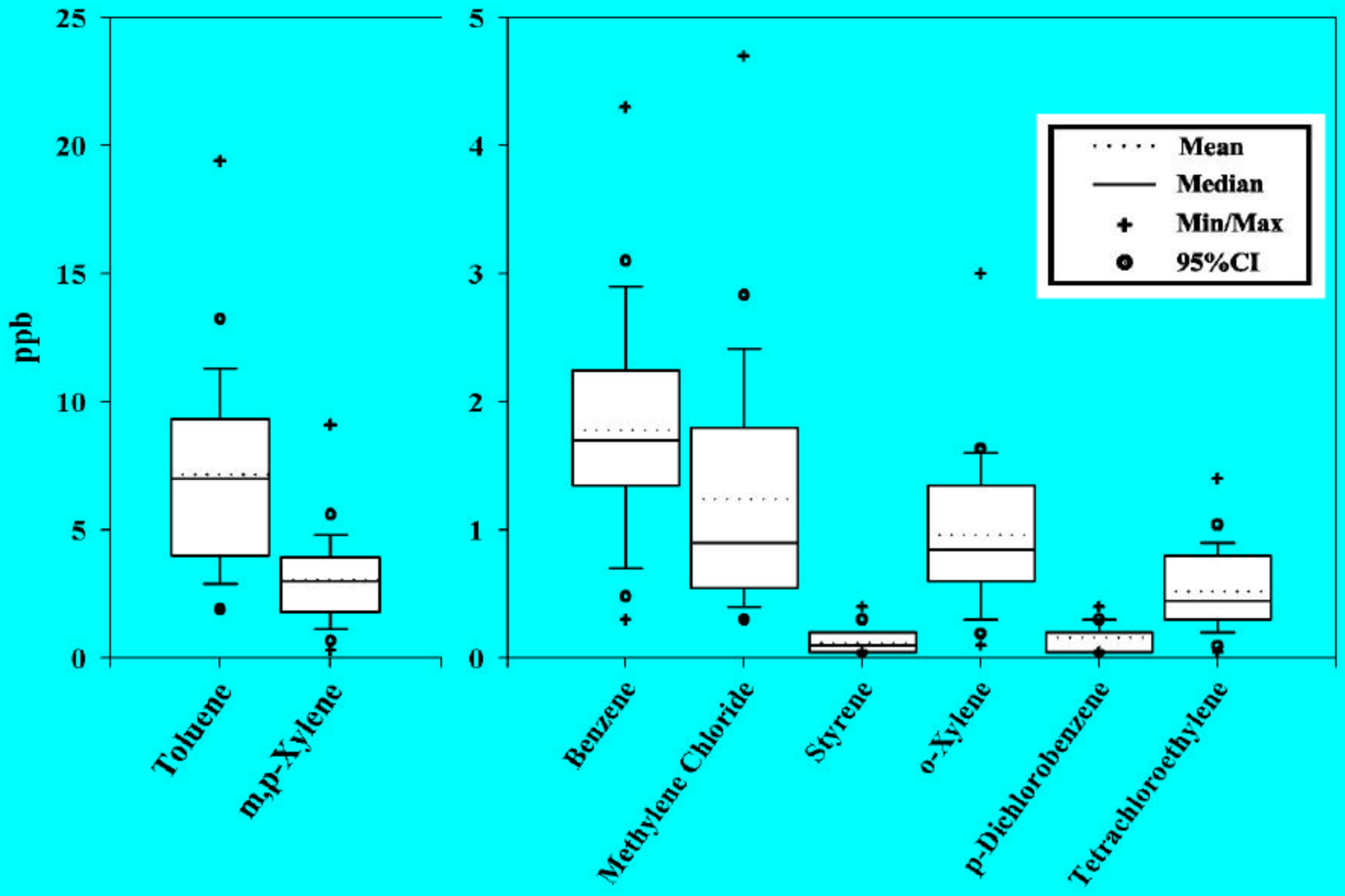
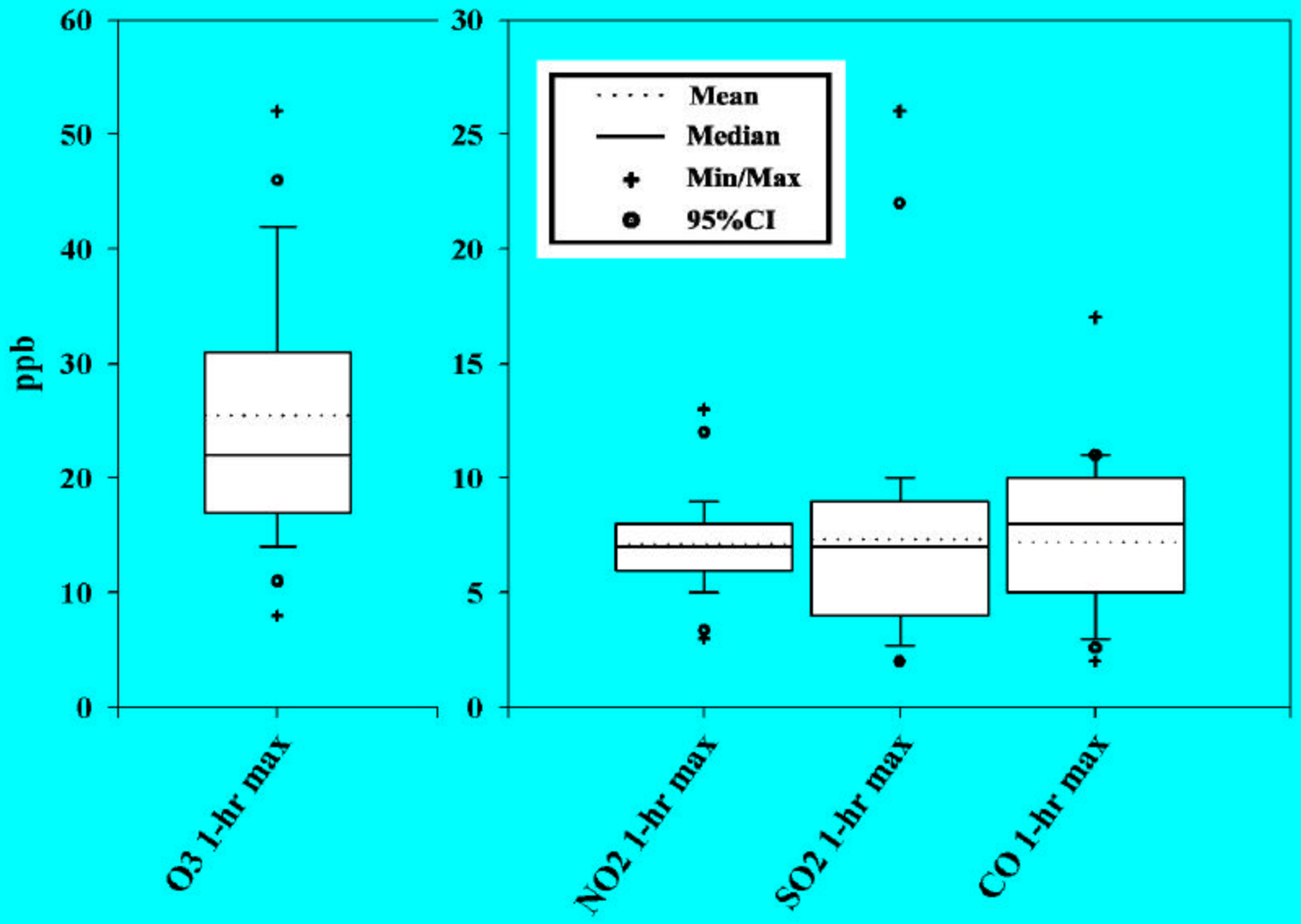
Ambient Air Pollution Exposures

- Outdoor 24-hr samples for non-carbonyl VOCs collected in XonTech 910A canisters, analyzed using EPA TO-14 methodology.
- Outdoor 24-hr air samples for carbonyls collected with XonTech 920 analyzed using EPA Method TO-11.
- Criteria air pollutant gases (O_3, NO_2, SO_2 and CO) measured continuously using EPA reference methods.
- Gravimetric 24-hr PM_{10} measured with quartz filters in a Sierra Anderson SSI hivol.
- Concentrations of EC-OC from PM_{10} filters analyzed using DRI Thermal/Optical Carbon Analyzer.

Box plot of ambient VOCs



Box plot of ambient criteria gases



VOC Exposure Assessment

- 3M 3530 organic vapor passive badges with a back-up section.
- Subset of 4 subjects.
- Personal samplers on collar of subjects.
- Indoor samplers placed in the bedroom.
- Exposure period 24 hrs.
- Analyzed with GC/MS.
- TAD data regressed on current & lagged VOCs

Figure. Scatter plot of personal versus indoor benzene

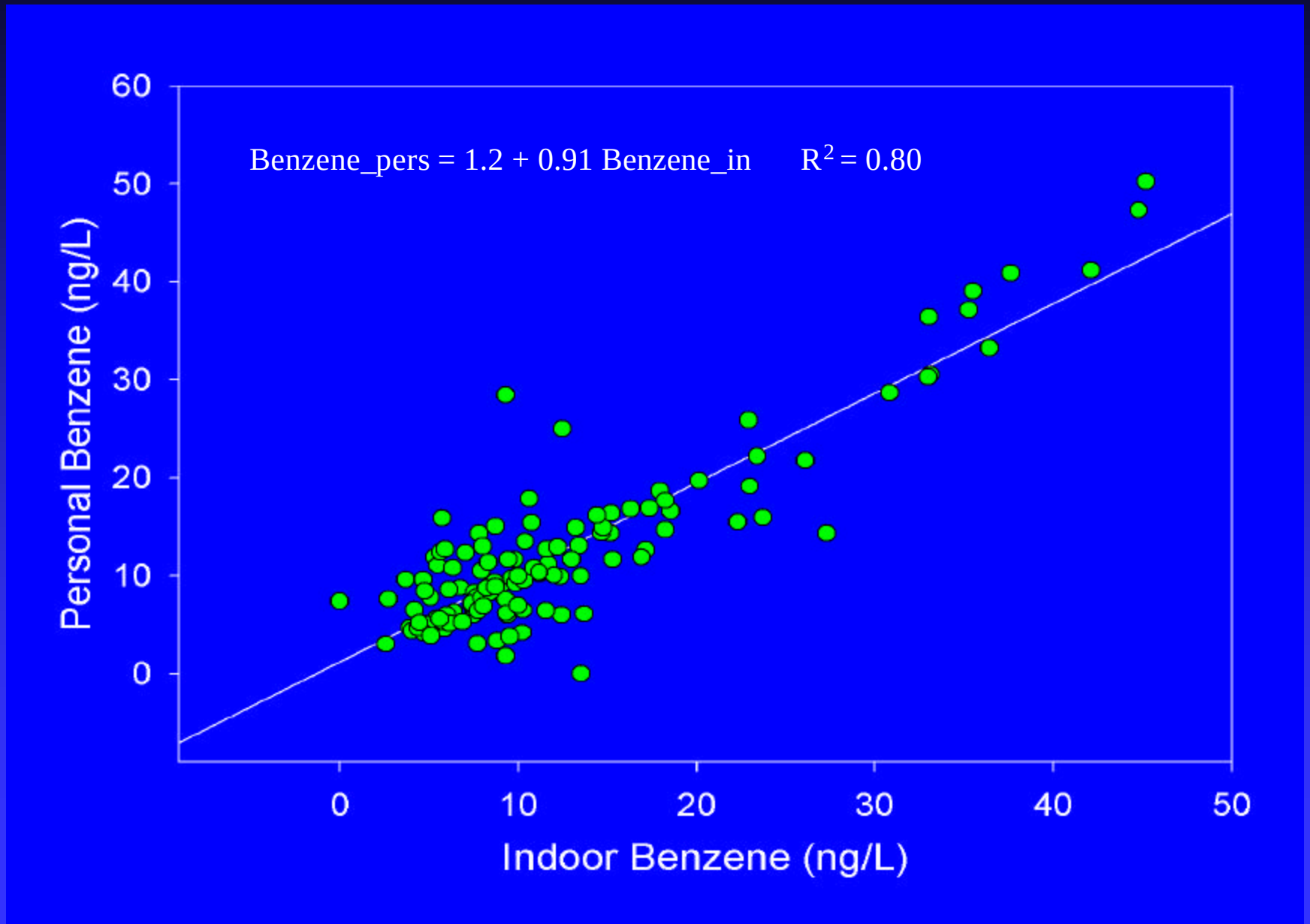
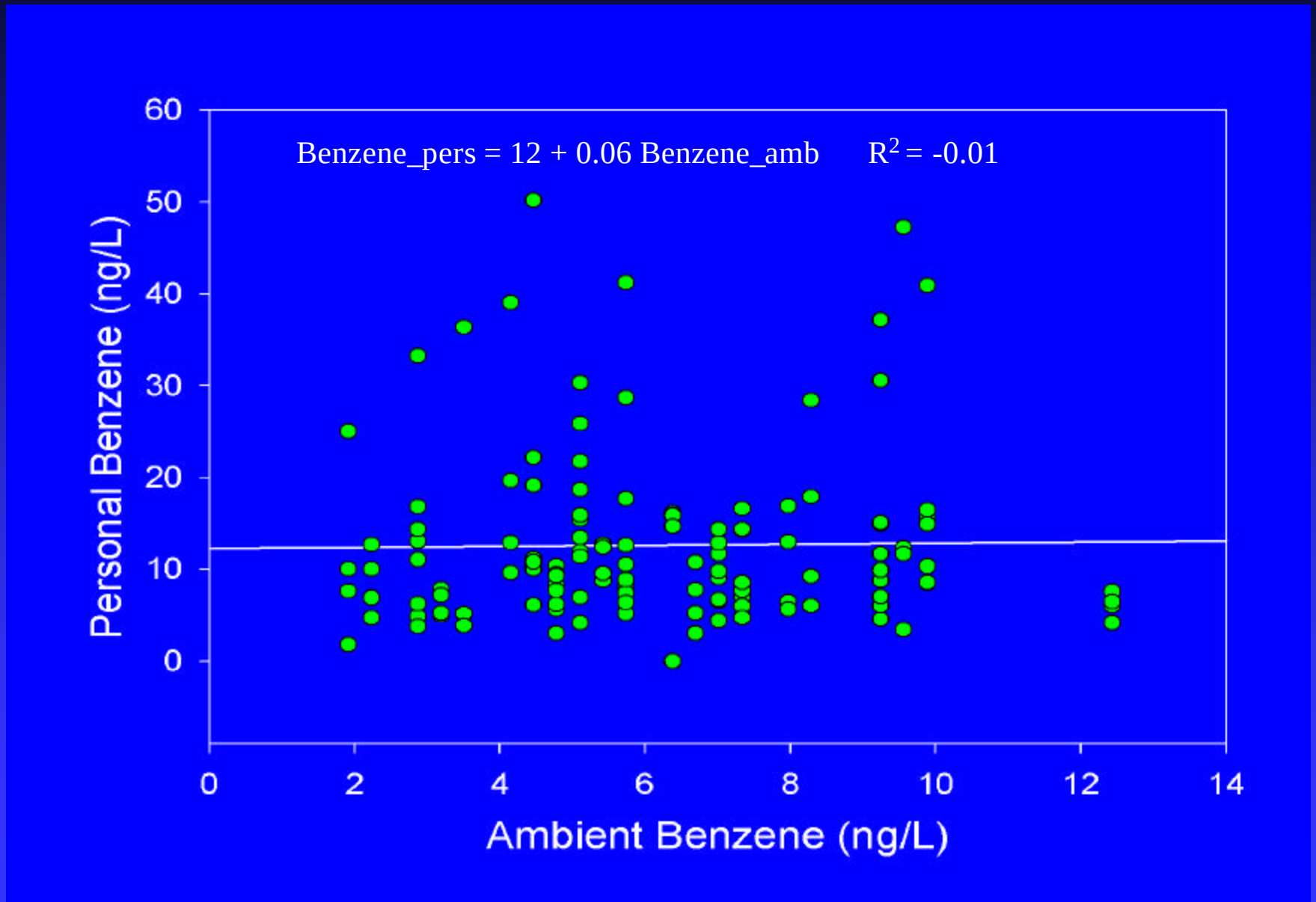


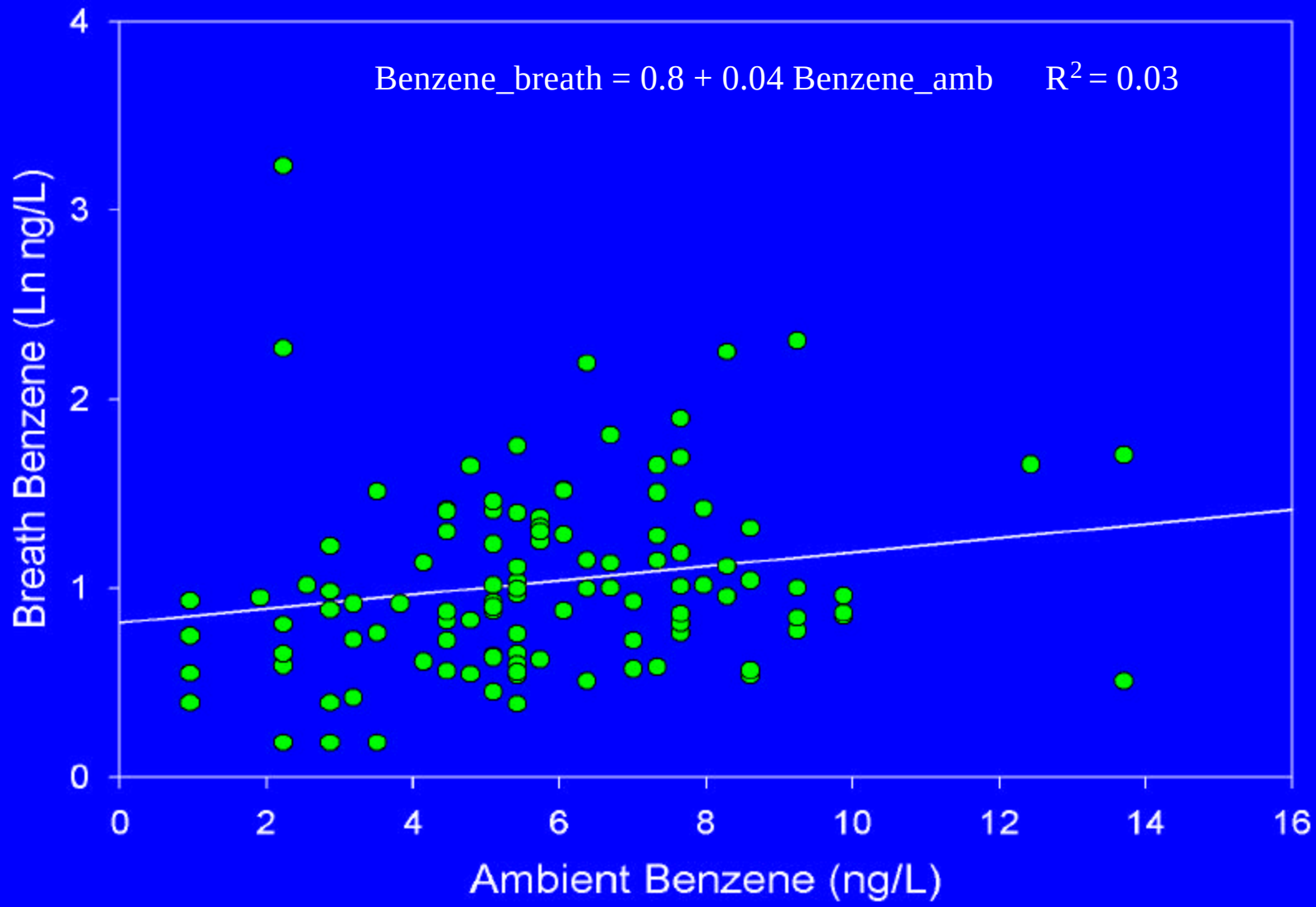
Figure. Scatter plot of personal versus ambient benzene



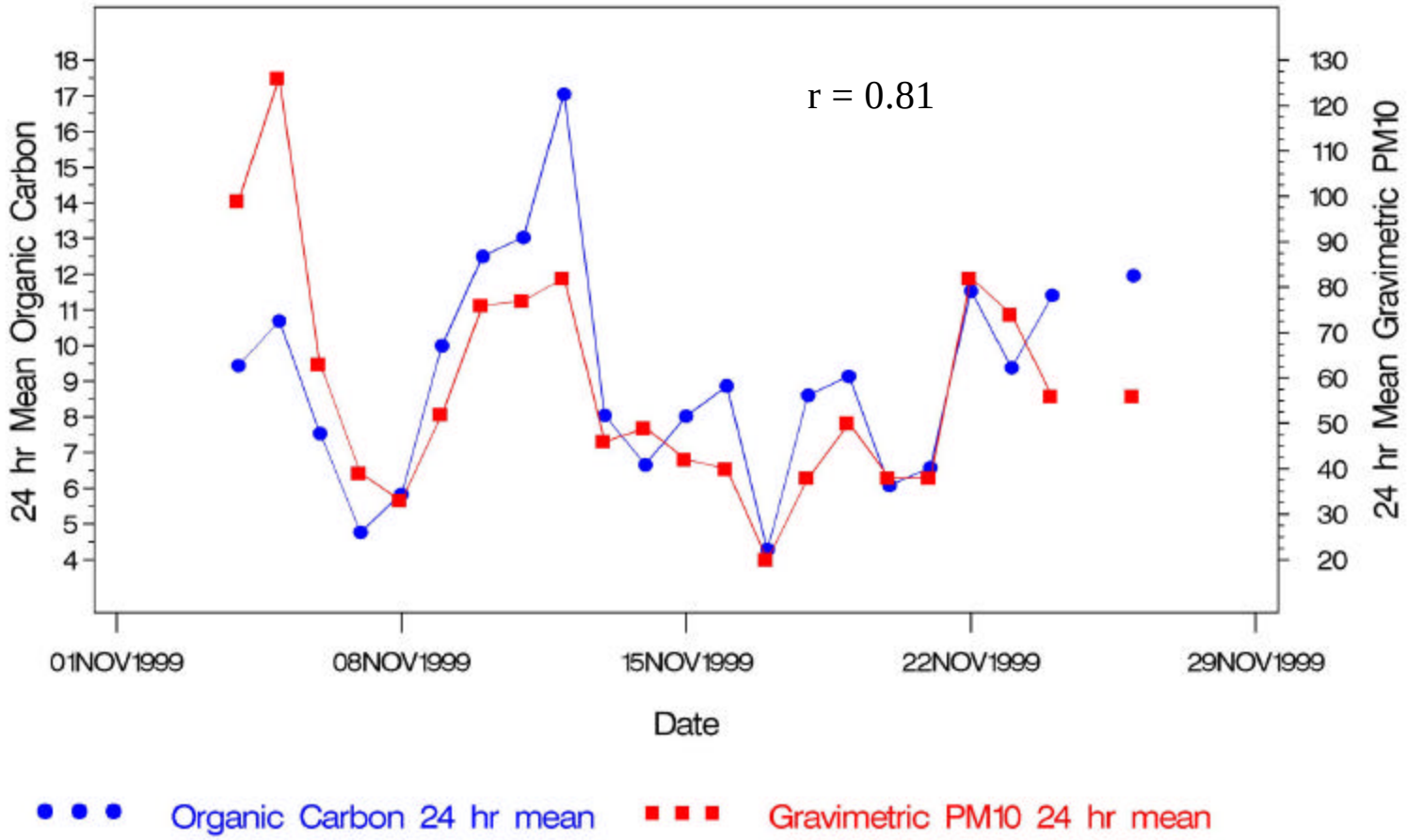
Selected Breath VOC Concentrations

	Mean (SD) (ng/L)	Median	Minimum / Maximum
Benzene	2.19 (2.72)	1.56	0.20 / 24.46
Toluene	8.28 (10.40)	5.70	2.00 / 69.68
m,*p*-Xylene	4.21 (5.98)	2.65	0.09 / 47.18

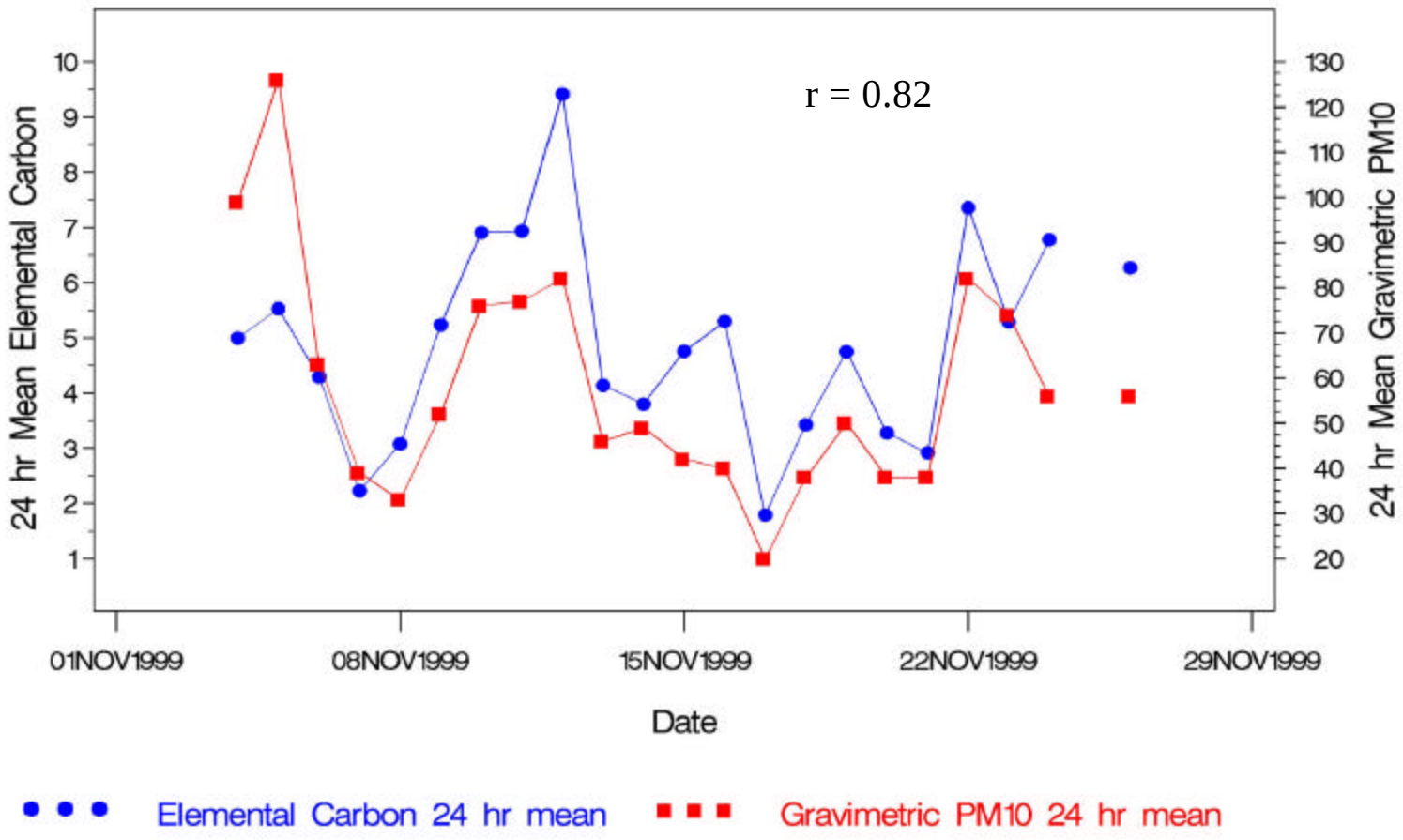
Figure. Scatter plot of breath versus ambient benzene



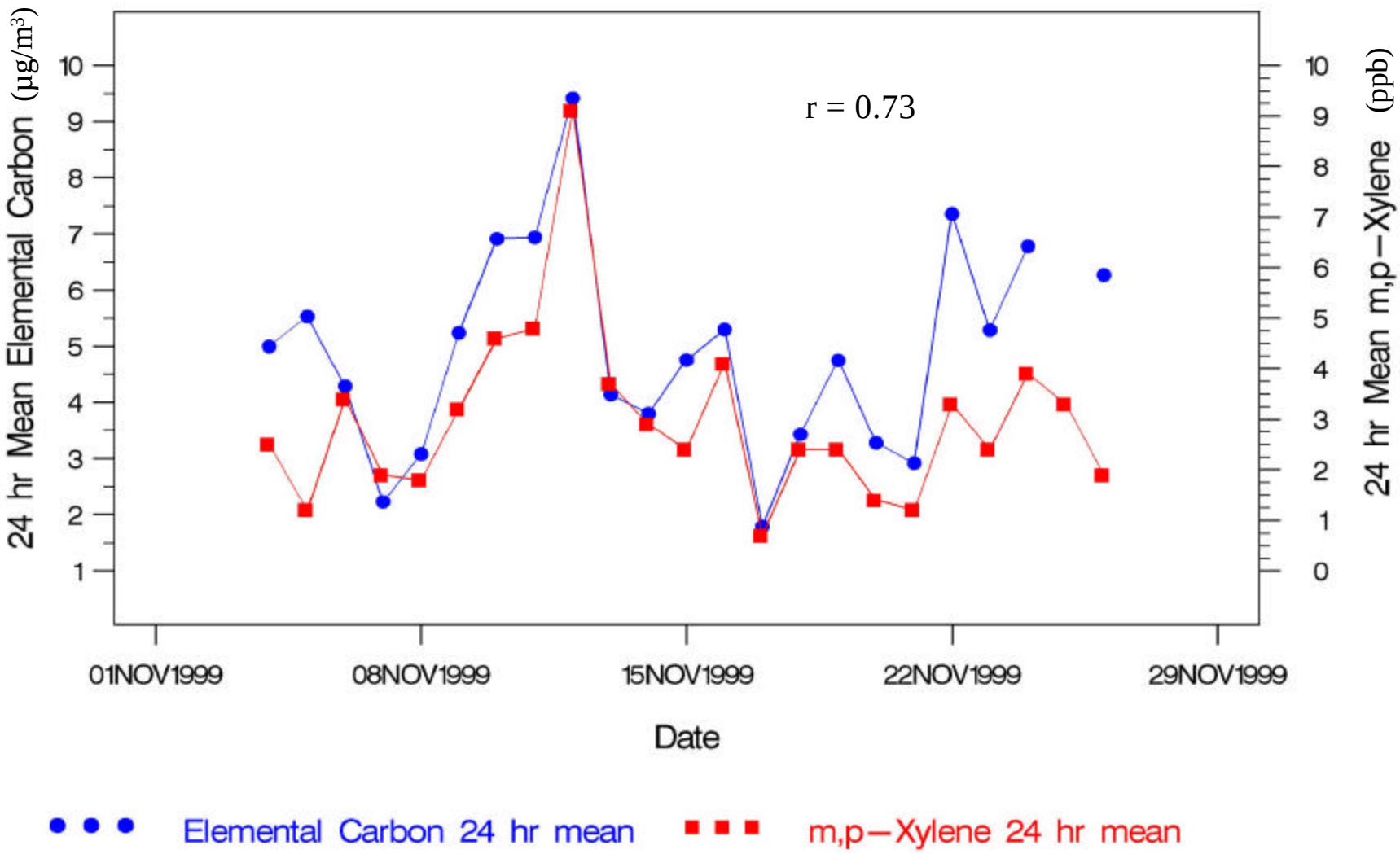
Time plot of daily 24-hr mean PM_{10} compared with the organic carbon fraction of PM_{10} ($\mu g/m^3$)



Time plot of daily 24-hr mean PM_{10} compared with the elemental carbon fraction of PM_{10} ($\mu g/m^3$)



Time plot of daily 24-hr mean PM_{10} elemental carbon compared with 24-hr mean *m,p*-xylene



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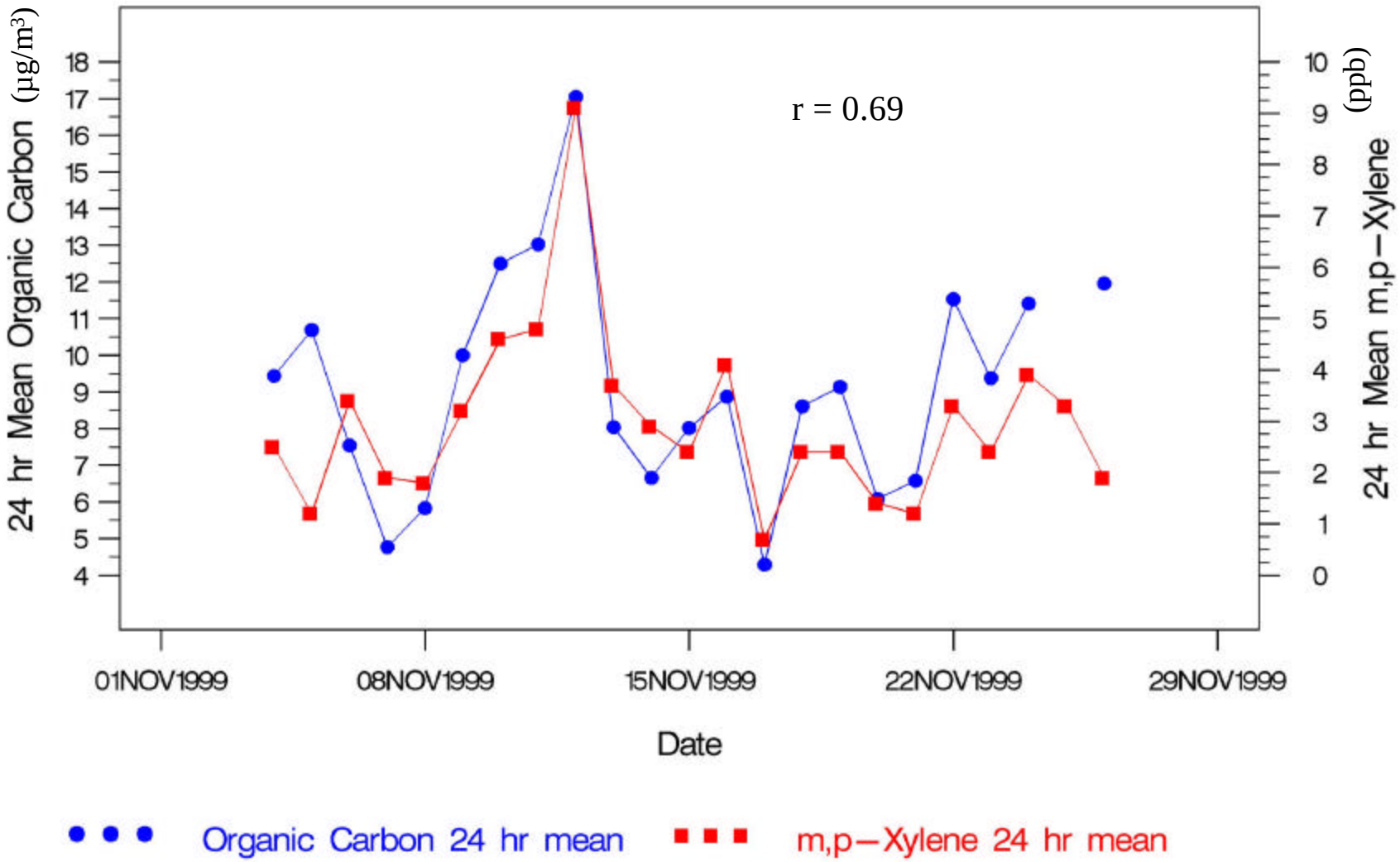


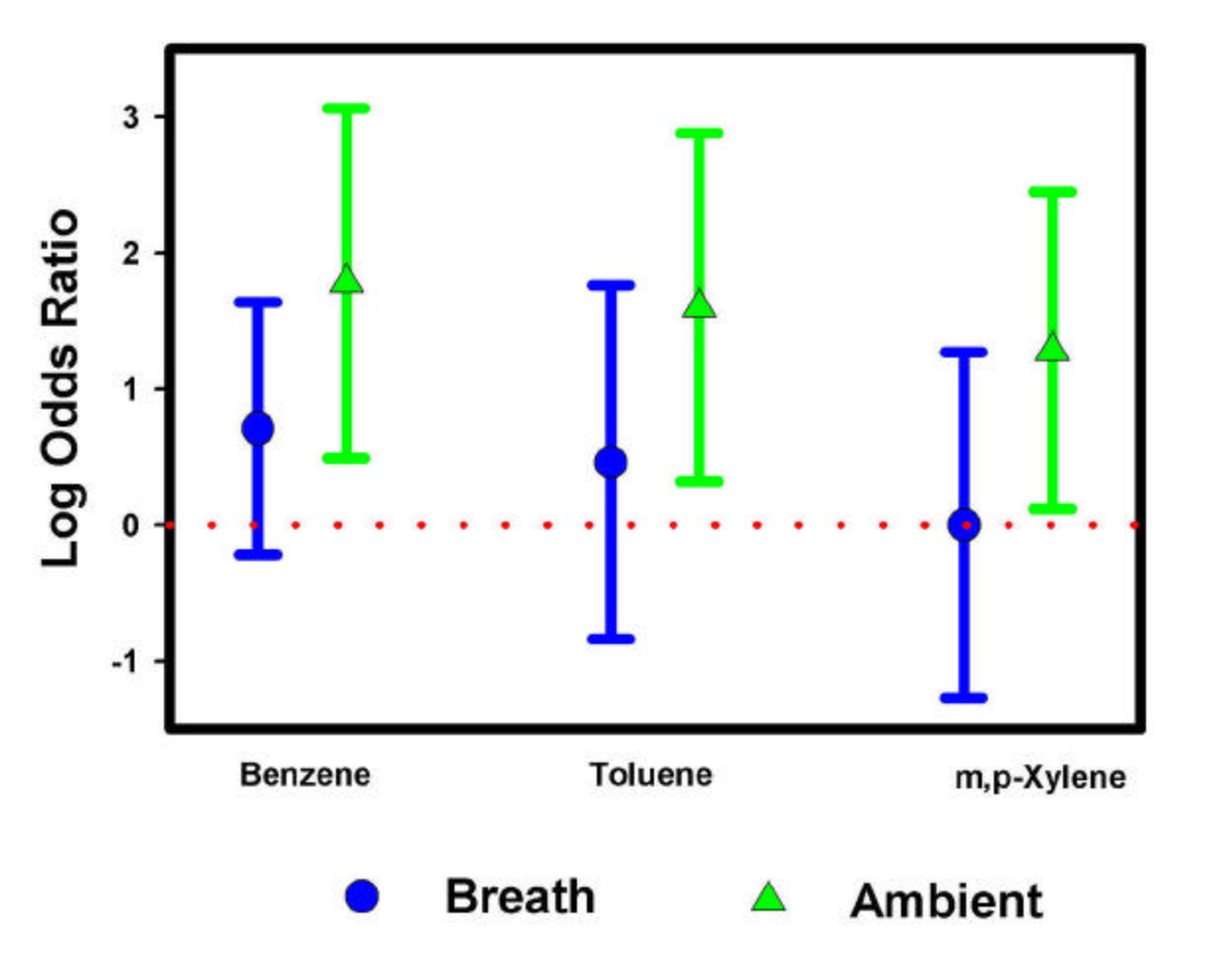
Regression Analysis

- Generalized Estimating Equations (GEE) for binary/ordinal asthma symptoms (SAS Proc GENMOD)
  - models covariance structure of correlated (not independent) measurements, an extension of GLIM for nonnormal repeated measures.
- Working correlation matrix (correlation of subject responses): Autoregressive (lag 1) or exchangeable correlation.
- Controlled for maximum temperature, respiratory infections.

Results for Asthma Symptoms and Breath vs. Ambient VOCs

- marginally positive associations between symptoms and same day breath benzene, but not other breath VOCs;
- symptoms more strongly associated with ambient petroleum-related VOCs measured on the same person-days as breath VOCs, including toluene, *m*,*p*-xylene, *o*-xylene, and benzene;
- symptoms were also associated with ambient NO_2 and SO_2 for the subset of breath sample days.

Relationship of asthma symptoms to VOCs measured in exhaled breath samples versus ambient outdoor central sites



Mean effects levels (ng/L): Benzene -- Br. 2.2, Amb. 5.7;
Toluene -- Br. 8.28, Amb. 27; *m,p*-xylene -- Br. 4.2, Amb. 13

Results for Daily Asthma Symptoms and Ambient Air Pollution

- We found positive associations of asthma symptoms with daily ambient exposures to:
  - criteria air pollutant gases (NO_2, SO_2)
  - Non-carbonyl VOCs (benzene, ethylbenzene, 1,3-butadiene, tetrachloroethylene, toluene, *mp*-xylene, and *o*-xylene).
  - Carbonyl VOCs (formaldehyde, acetaldehyde, acetone)
  - PM_{10}, EC-OC fractions of PM_{10}.

Symptoms and Daily Ambient Lag 0 Criteria Pollutant Gases

Pollutant variable	Interquartile Range (IQR) (ppb)	Odds Ratio (95% CI) at IQR of Pollutant
NO_2 8-hr max	1.4	1.27 (1.05, 1.54)
SO_2 8-hr max	2.5	1.23 (1.06, 1.41)
CO 8-hr max	3.0	0.95 (0.55, 1.62)
O_3 8-hr max	10.8	0.90 (0.60, 1.36)

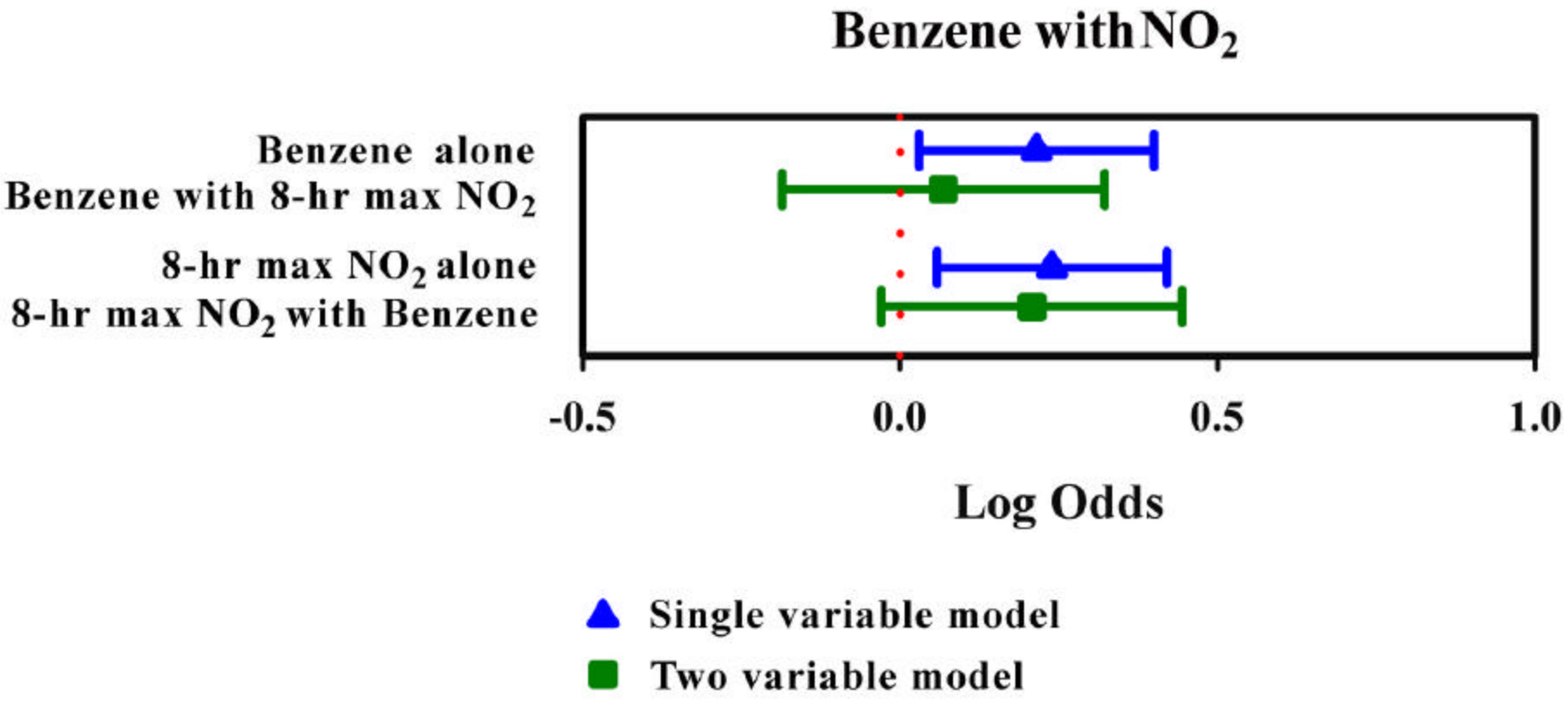
Symptoms and Daily Ambient Lag 1 Carbonyl VOCs

Pollutant variable	Interquartile Range (IQR) (ppb)	Odds Ratio (95% CI) at IQR of Pollutant
Acetaldehyde	1.31	1.48 (1.16, 1.87)
Acetone	5.39	1.13 (0.80, 1.60)
Formaldehyde	3.16	1.37 (1.04, 1.80)

Symptoms and Daily Ambient Lag 0 non-Carbonyl VOCs

Pollutant variable	Interquartile Range (IQR)	Odds Ratio (95% CI) at IQR of Pollutant
Benzene	1.00	1.23 (1.02, 1.48)
Ethylbenzene	0.50	1.38 (1.09, 1.75)
Tetrachloroethylene	0.40	1.37 (1.09, 1.71)
Toluene	4.90	1.35 (0.99, 1.84)
m,*p*-Xylene	2.20	1.35 (1.01, 1.80)
o-Xylene	0.70	1.28 (1.00, 1.66)

Single vs. two-pollutant regression models of a VOC and a criteria pollutant gas



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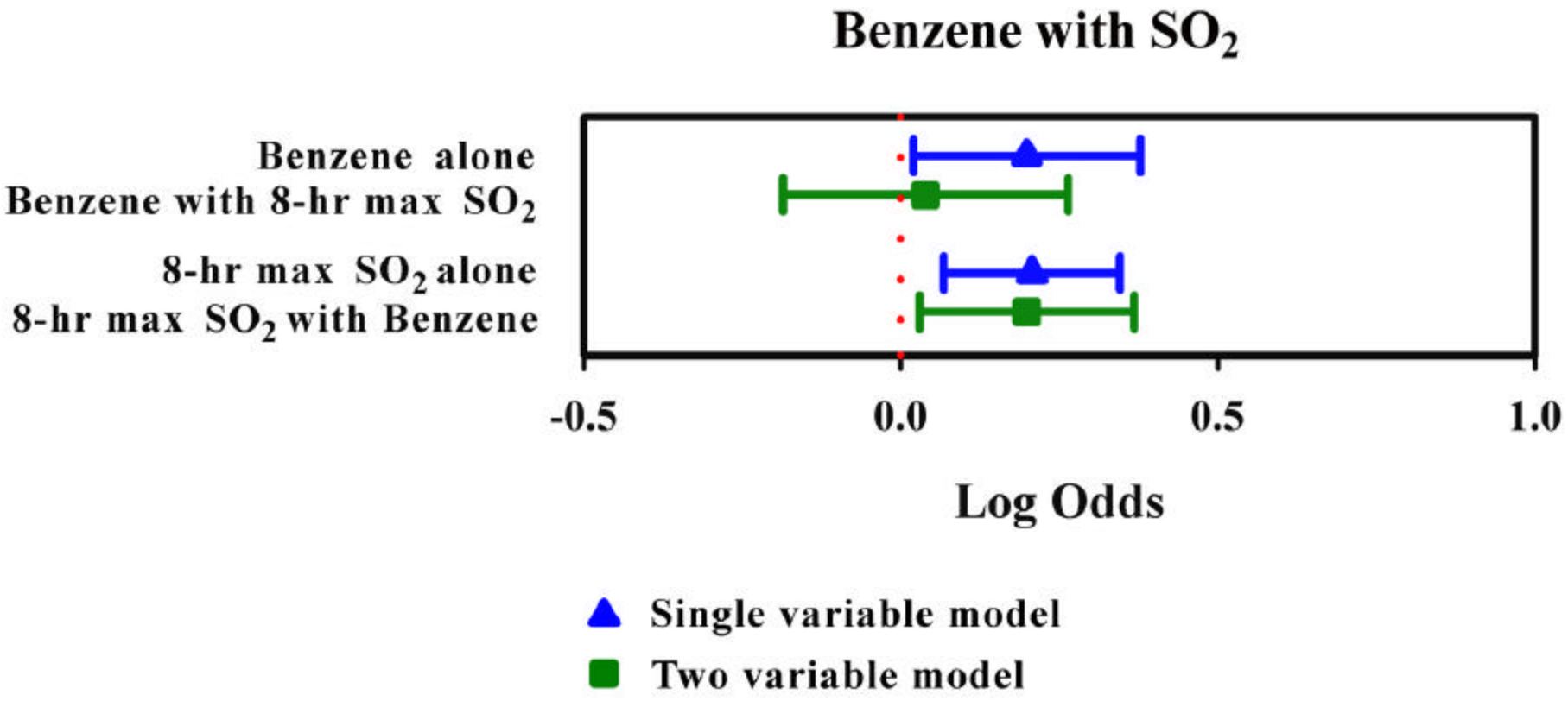

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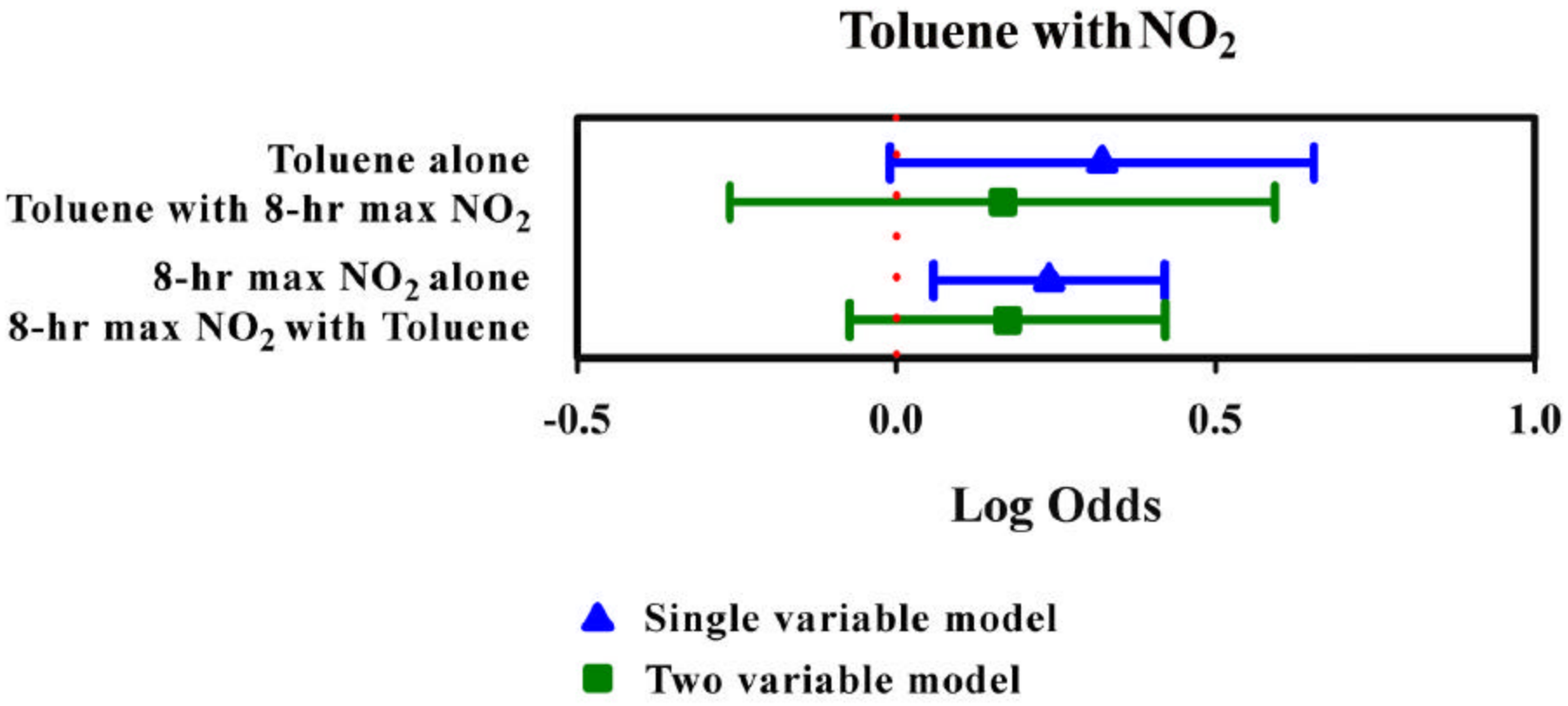

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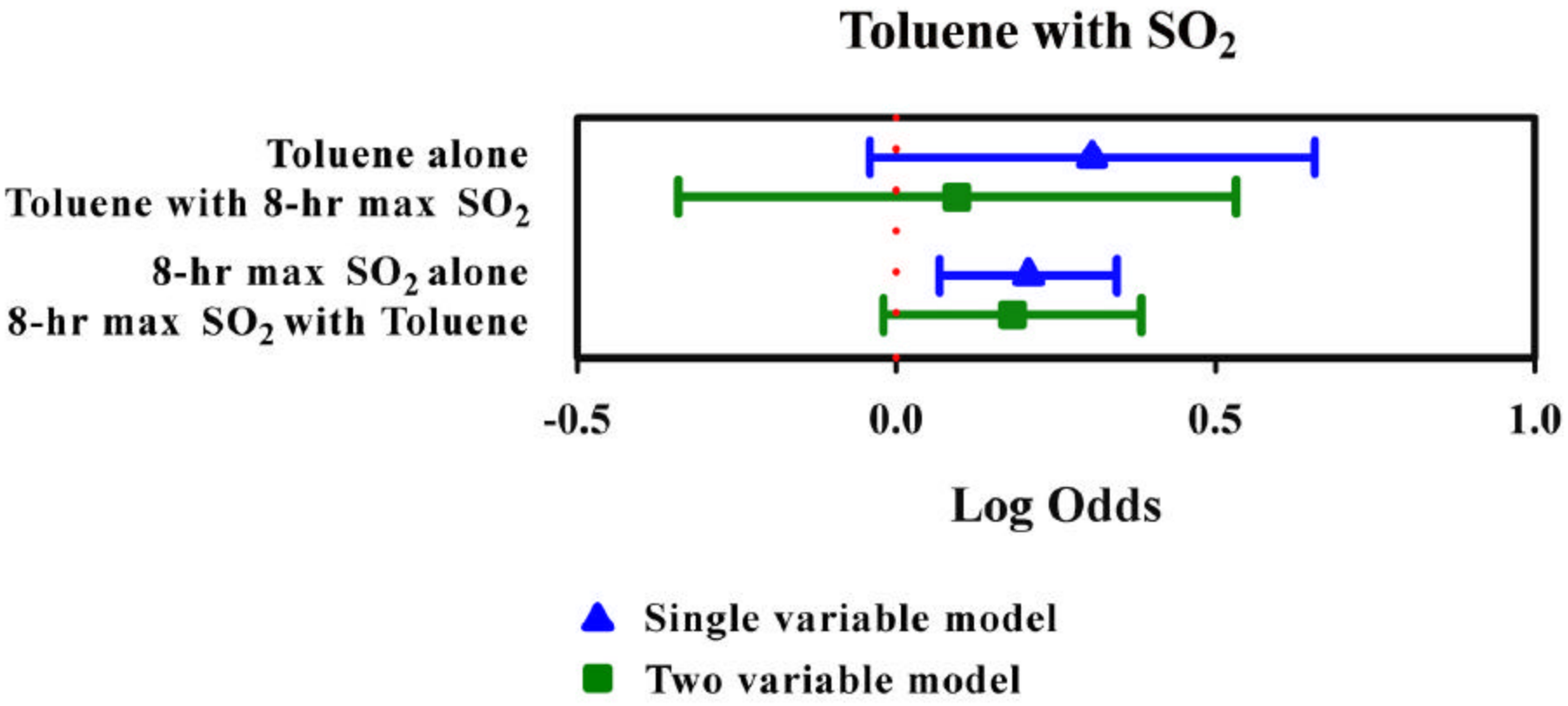

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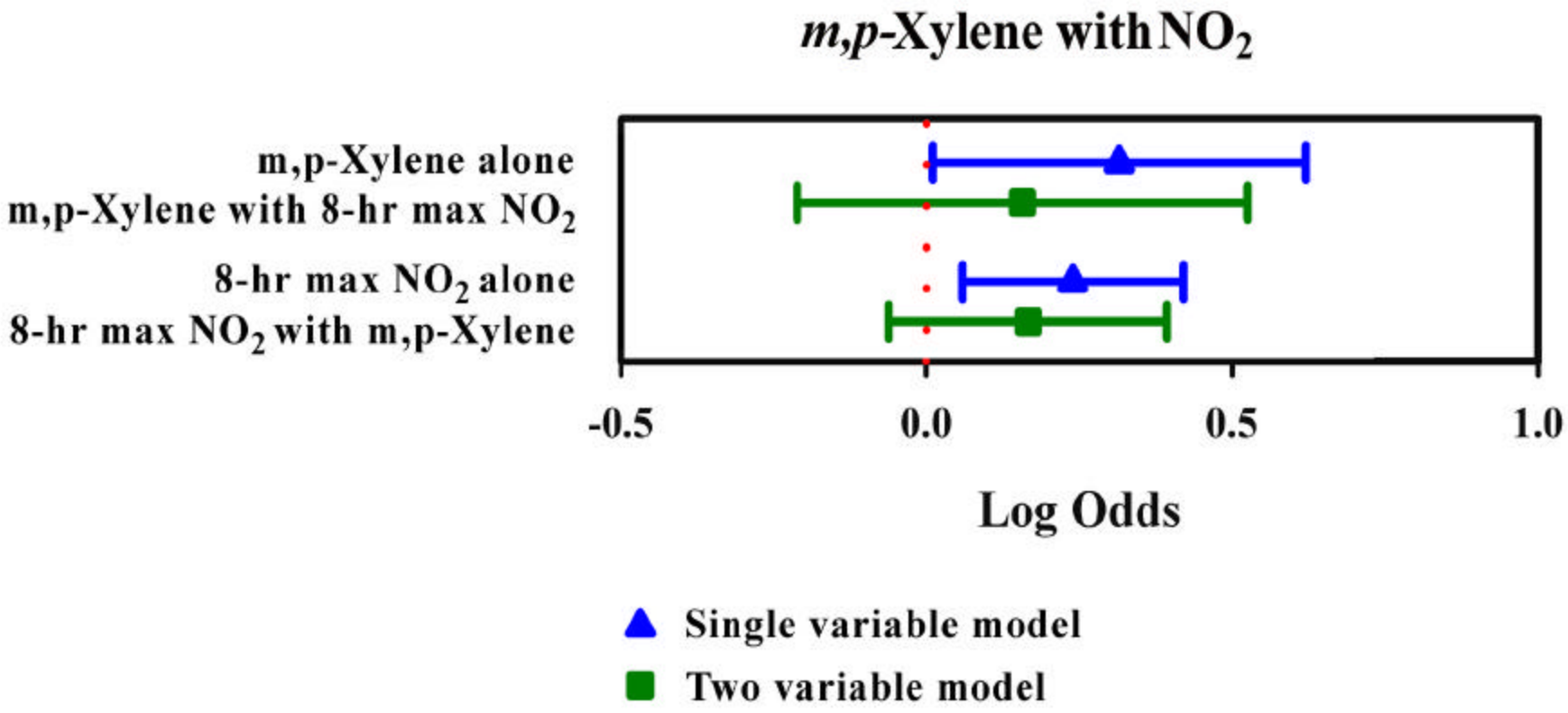

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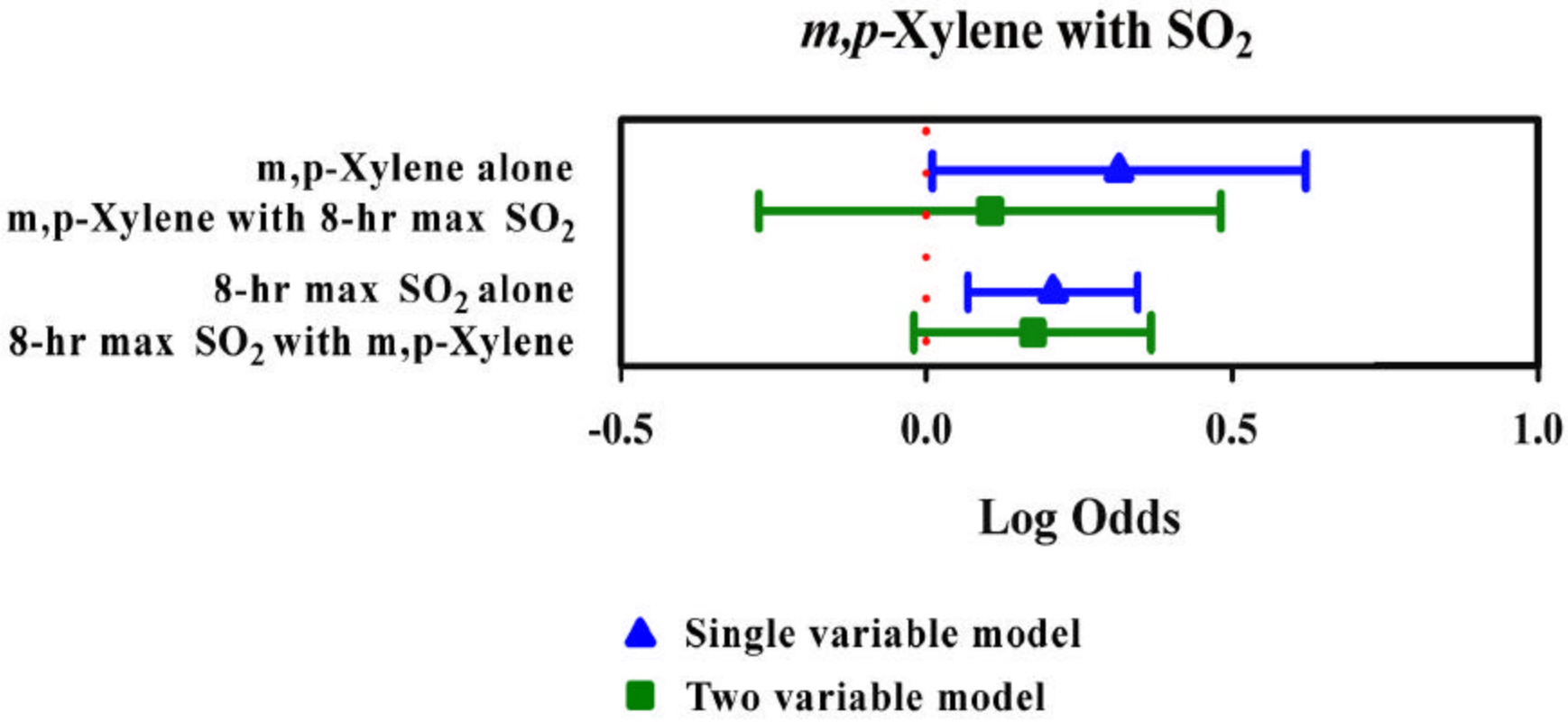

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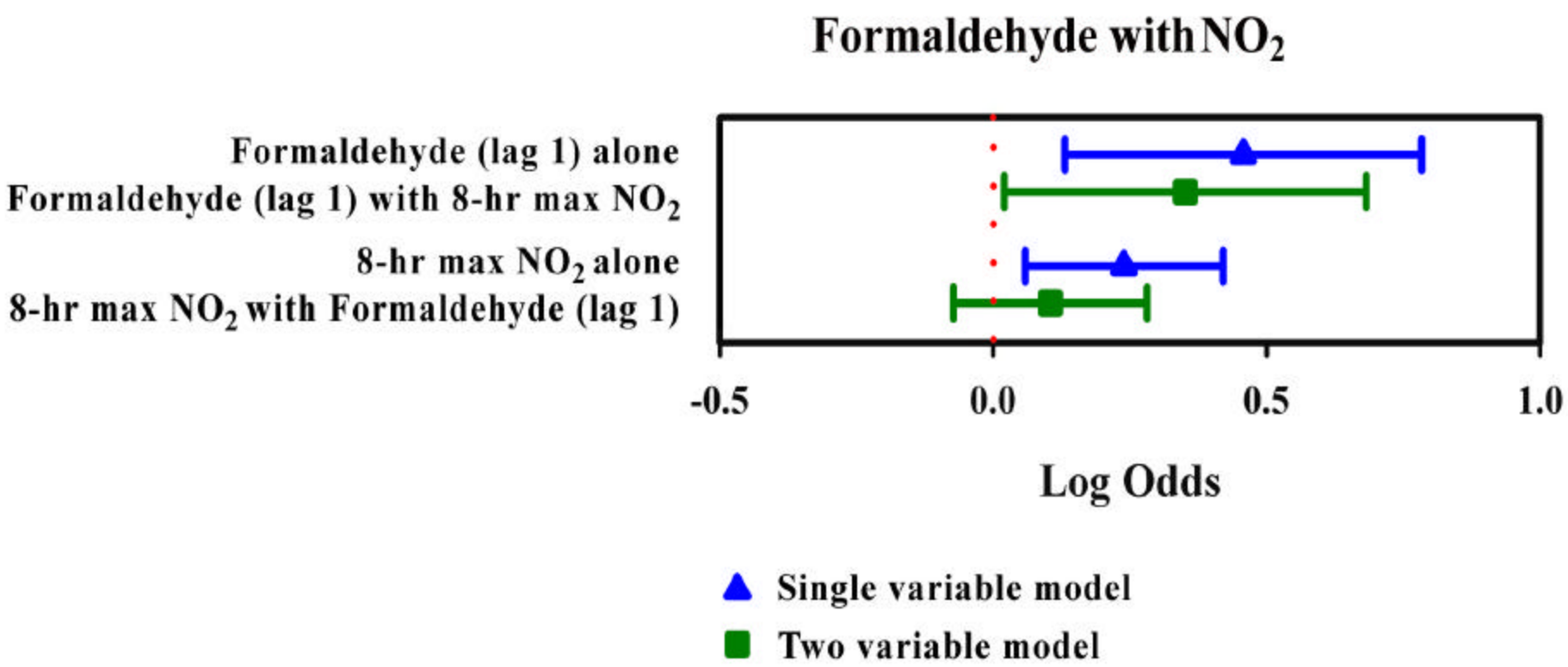

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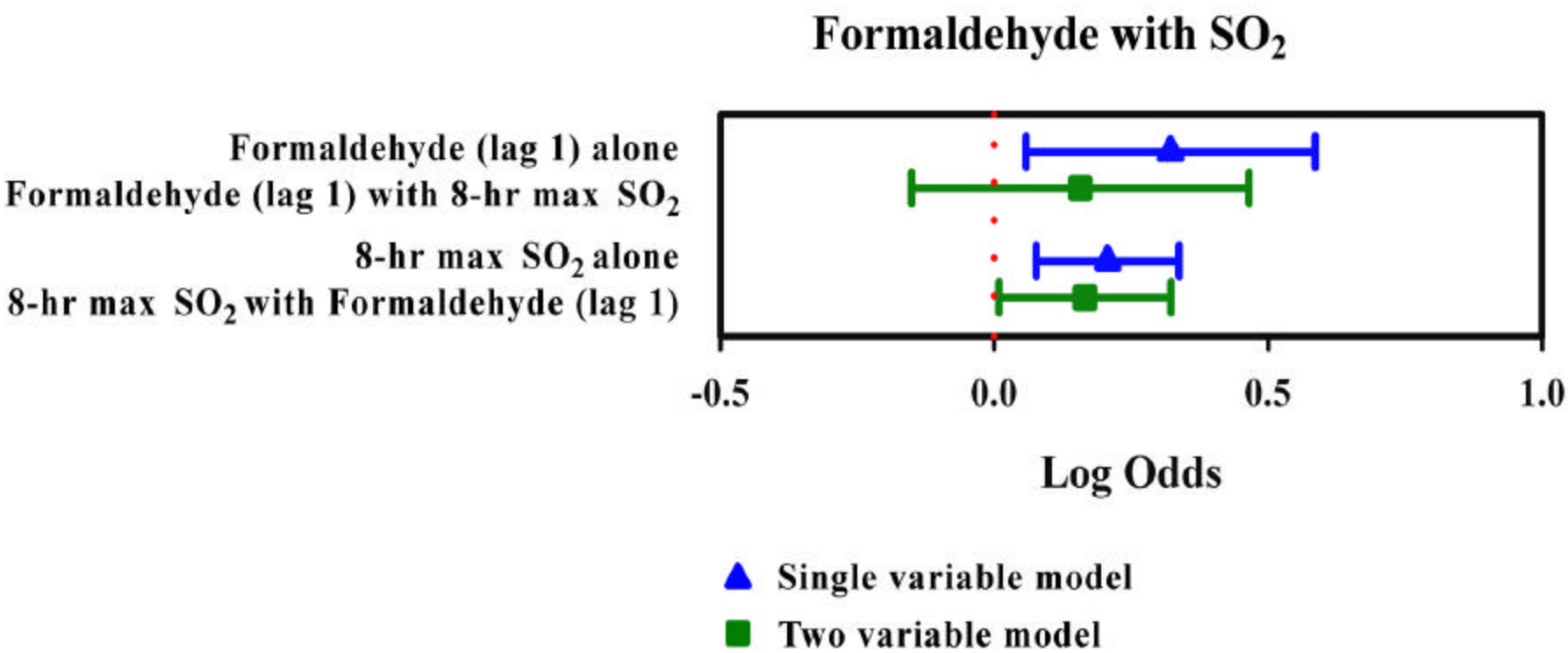

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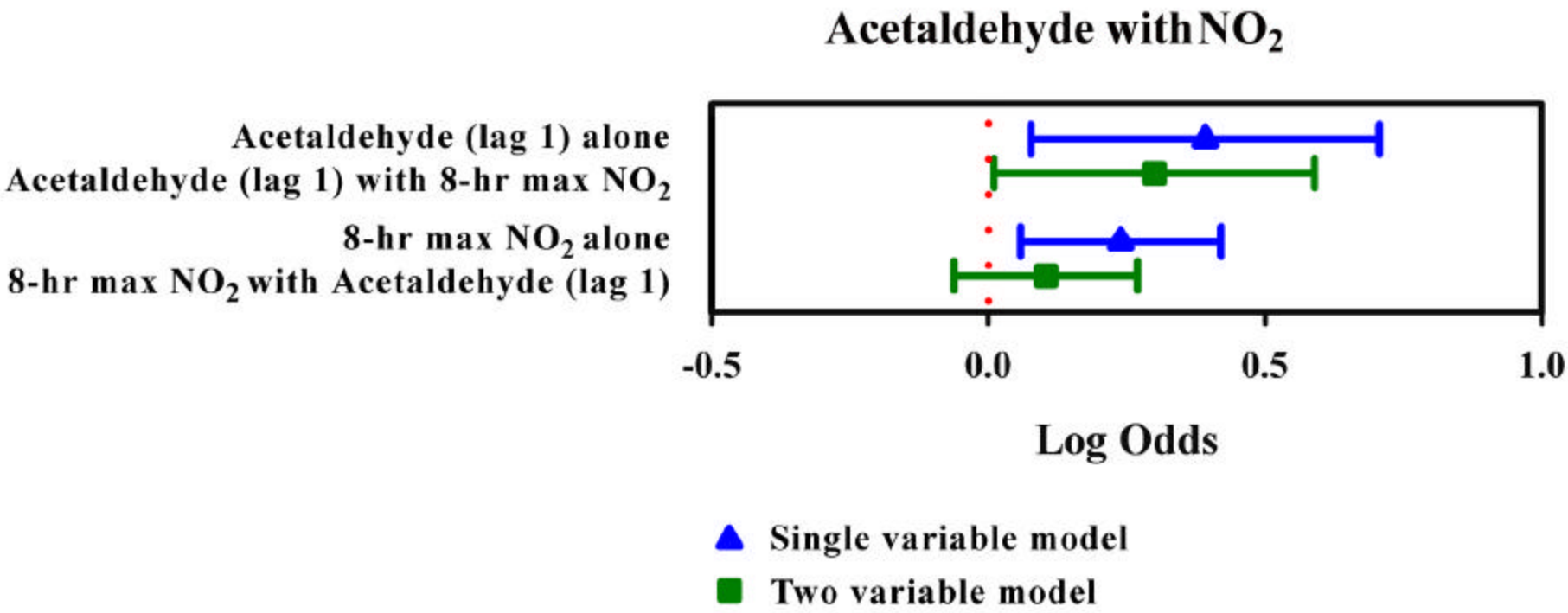
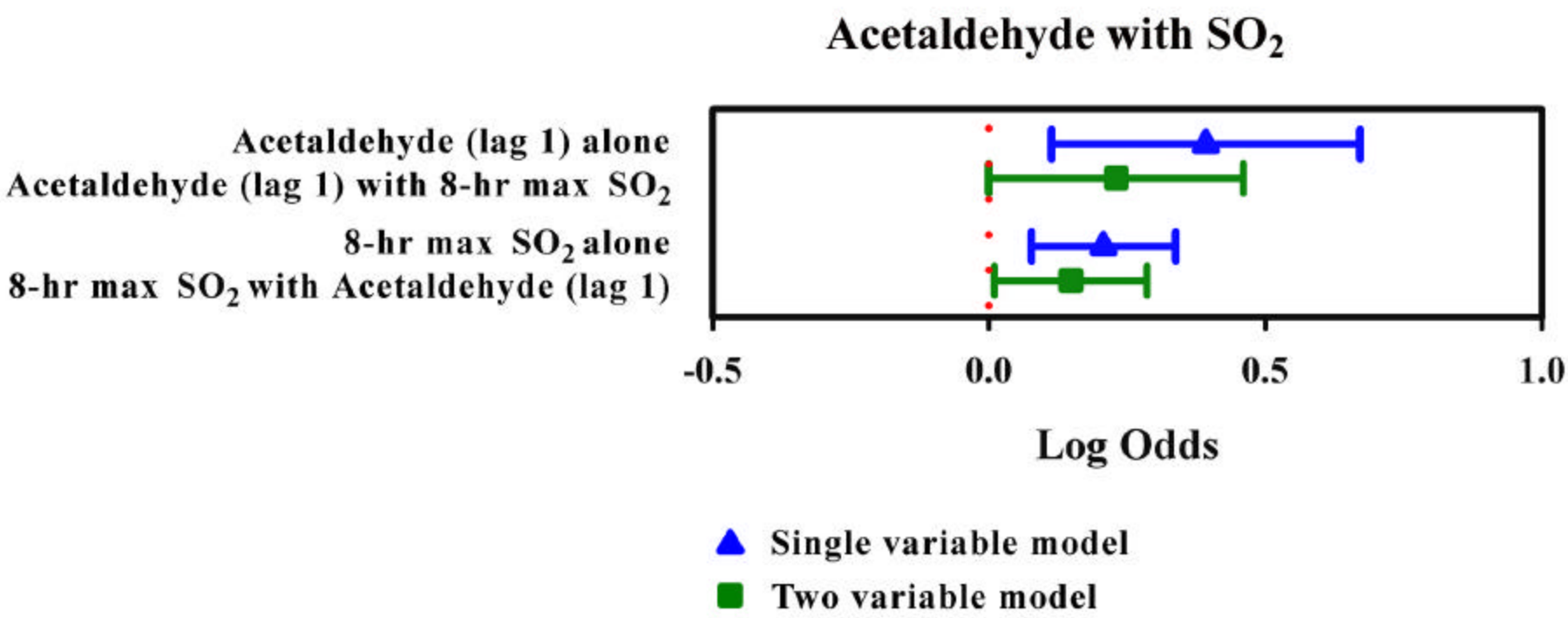


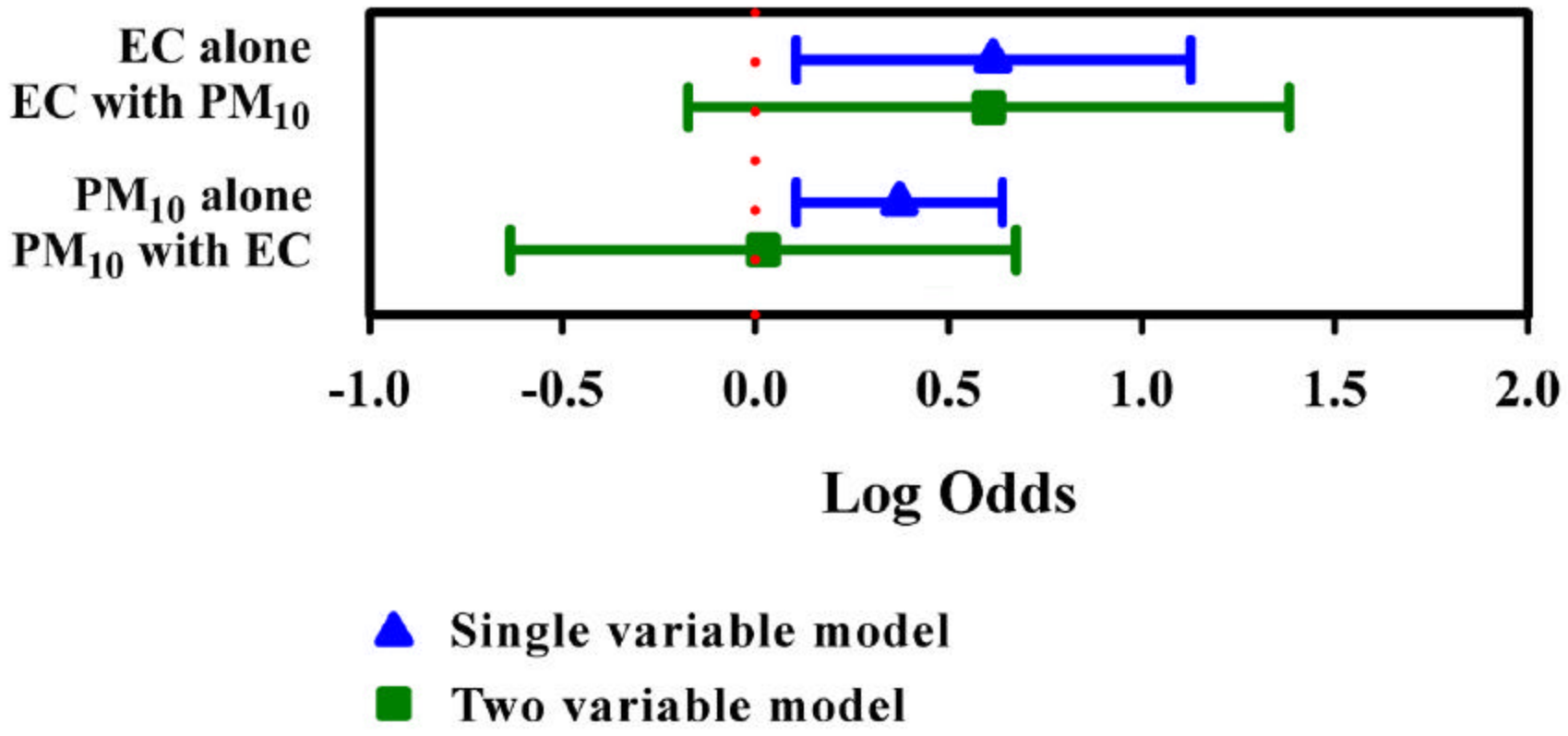
Single vs. two-pollutant regression models of a VOC and a criteria pollutant gas



Associations of Asthma Symptoms with PM

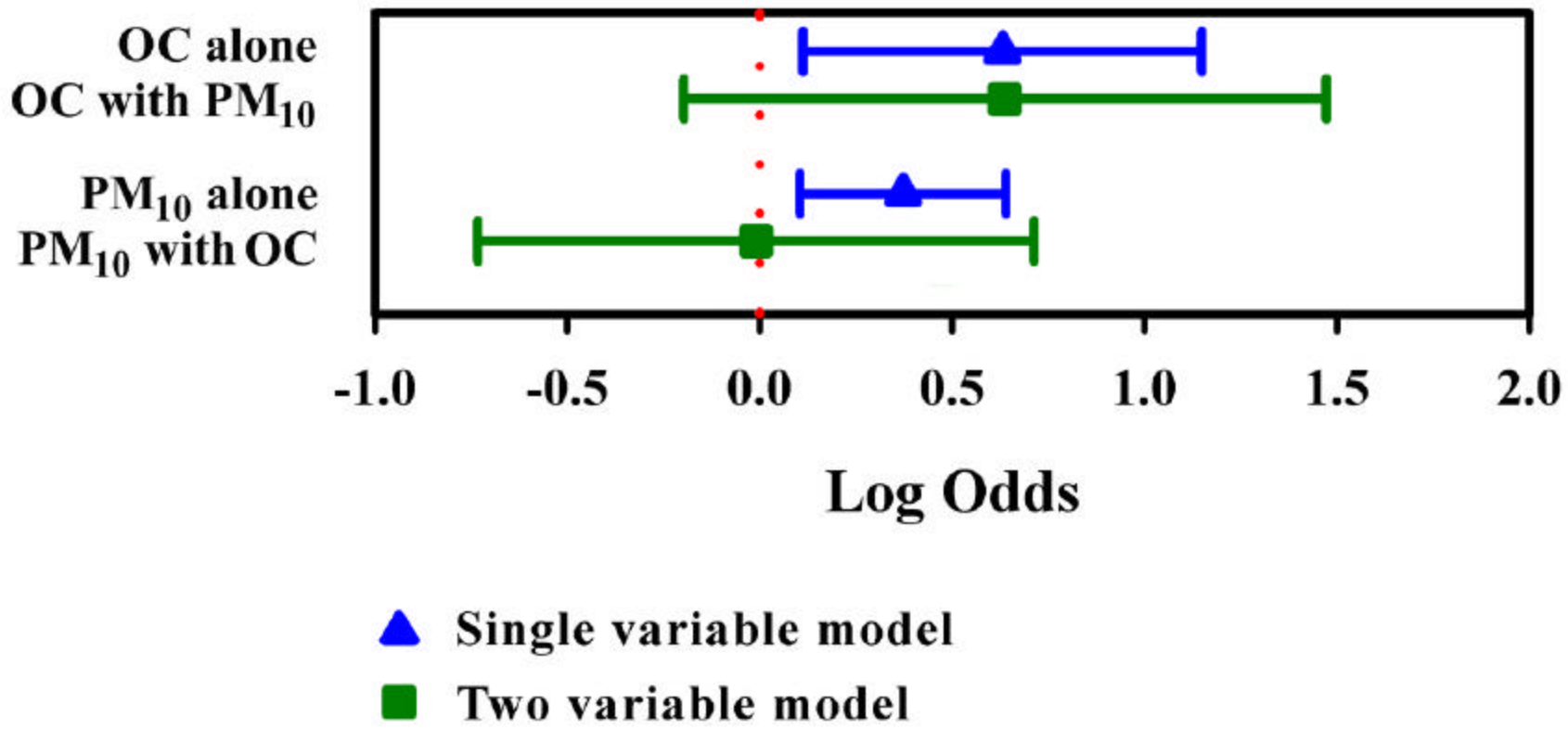
	Interquartile Range (IQR)	Odds Ratio at IQR	95% CI
PM_{10}	37.0 μg/m^3	1.45	1.11, 1.90
EC	2.91 μg/m^3	1.85	1.11, 3.08
OC	4.64 μg/m^3	1.88	1.12, 3.17

Relationship of asthma symptoms to lag 0 PM_{10} and the elemental carbon fraction of PM_{10}



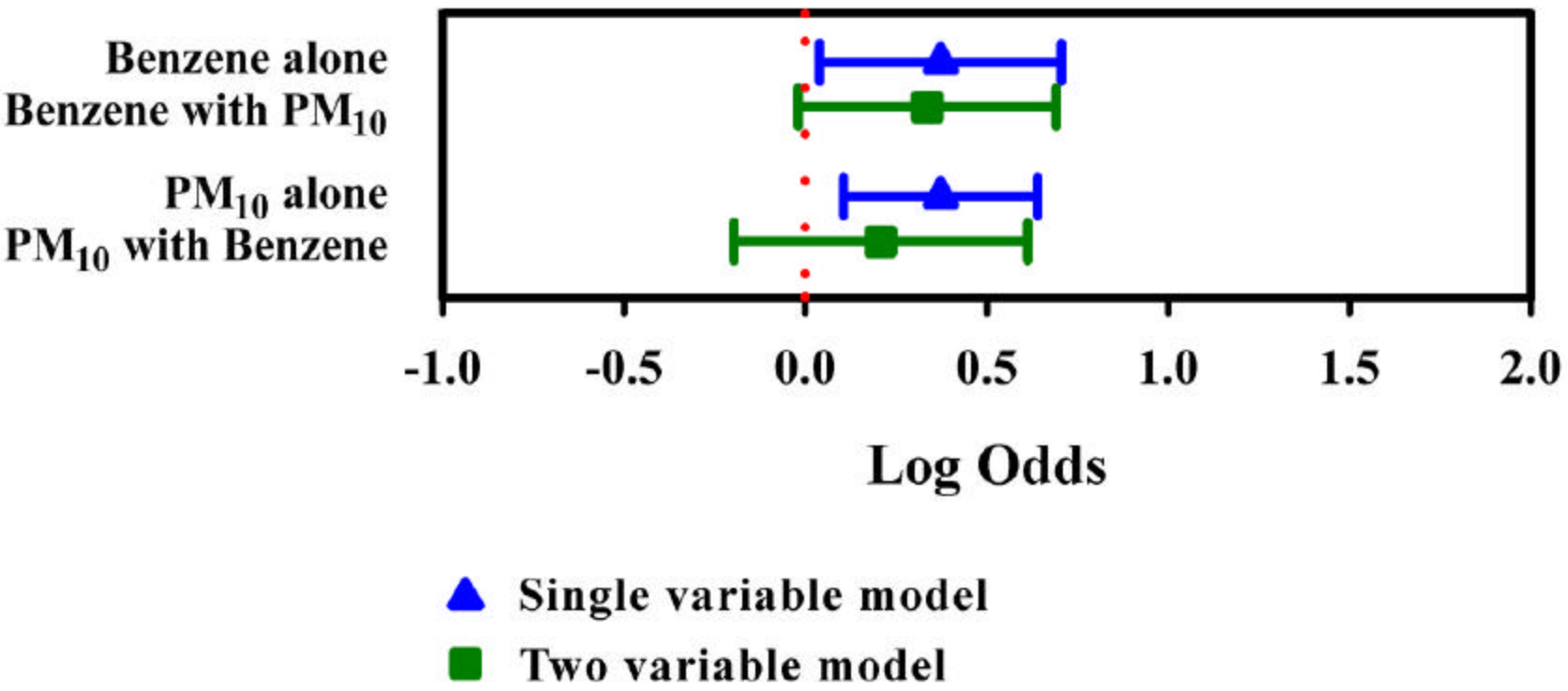
Log odds at interquartile range: 37.0 µg/m^3 PM_{10}; 2.91 µg/m^3 EC

Relationship of asthma symptoms to lag 0 PM_{10} and the organic carbon fraction of PM_{10}



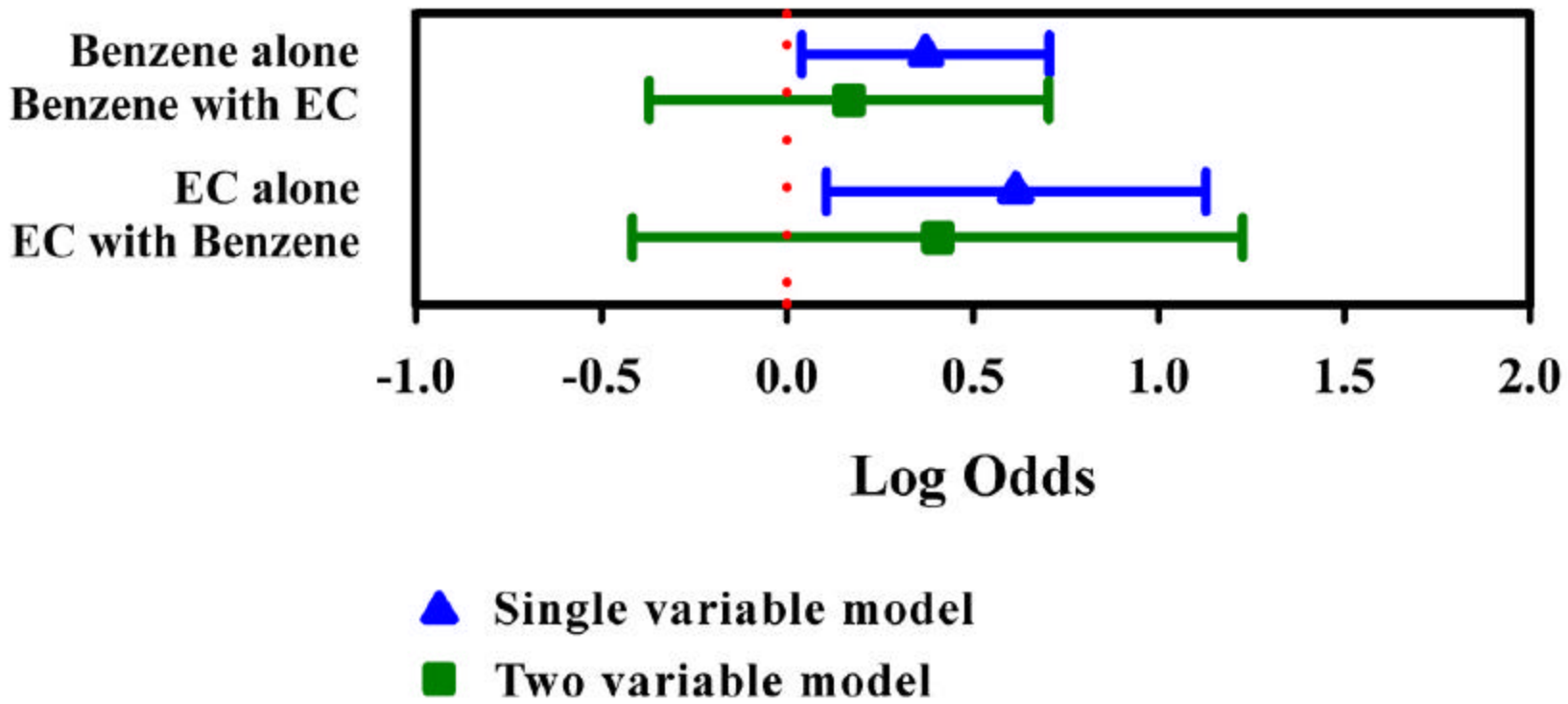
Log odds at interquartile range: 37.0 µg/m^3 PM_{10}; 4.64 µg/m^3 OC

Relationship of asthma symptoms to lag 0 PM_{10} and benzene



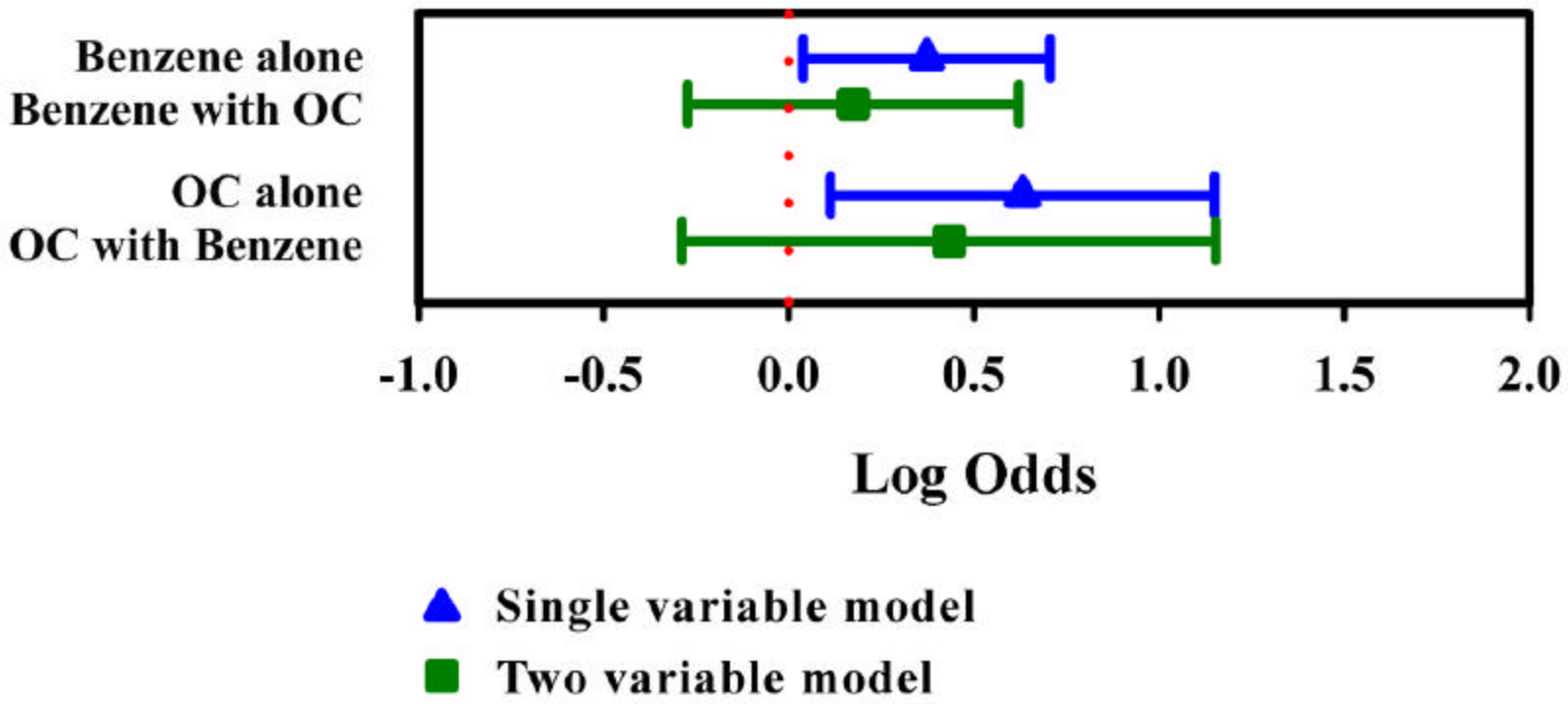
Log odds at interquartile range: Benzene 1.00 ppb; 37.0 µg/m^3 PM_{10};

Relationship of asthma symptoms to lag 0 elemental carbon fraction of PM_{10} and benzene



Log odds at interquartile range: Benzene 1.00 ppb; 2.91 µg/m^3 EC

Relationship of asthma symptoms to lag 0 organic carbon fractions of PM_{10} and benzene



Log odds at interquartile range: Benzene 1.00 ppb; 4.64 µg/m^3 OC

Discussion

- Associations for Breath vs. Ambient VOC.
- Associations for criteria air pollutant gases vs. VOCs.
- Associations for PM_{10} mass vs. EC and OC.
- New Directions

Hypotheses to explain stronger associations for ambient than breath VOCs

- ambient VOC measurements may be serving as better surrogates for true causal air pollutants in outdoor air.
  - breath VOCs, like personal VOC exposures, are weakly correlated with outdoor levels;
- breath concentrations may less accurately reflect pulmonary doses during the time frame relevant to responses; and/or
- weak causal strengths of VOCs were not detected by small N of breath VOCs, while biases led to associations with ambient VOCs for breath sample person-days.

Criteria gases vs. VOCs

- Associations for SO_2 and NO_2 found at low concentrations.
- Experimental evidence for VOCs is limited.
- Evidence that NO_2 or SO_2 confounded VOC effects was weak, inconsistent and clouded by multicollinearity.
- Log odds for formaldehyde and acetaldehyde were more stable than NO_2, and remained significantly associated with symptoms.

PM_{10} mass vs. EC and OC

- Particle mass association is consistent with other asthma panel studies.
- New evidence: particle associations were better explained by EC and OC than by PM_{10}
- Organic compounds such as PAHs may have driven particle associations.
- Most EC-OC is in the fine fraction < 2.5 µm
- Findings for mass vs. EC-OC may have been different had $PM_{2.5}$ been used.

Conclusion, Huntington Park Study

Some of the VOCs, NO_2, SO_2, OC and EC may all be markers for a causal mixture of traffic-related pollutants in an area with high traffic density.

Our findings in asthmatic children may have been due to the pro-inflammatory and irritant nature of these traffic-related pollutants .

New directions

- More extensive evaluation of:
  - exposures to other air toxics: PAH;
  - personal exposures, including assessments of exposures to air toxics of outdoor origin;
  - potential of PM to generate ROS.
- Compare relationships for $PM_{2.5}$ mass vs EC-OC
- Assessments of biomarkers of inflammation;
- Advancement in the use of biomarkers of toxic air pollutant exposures.