Title: Associations between Personal Exposures to VOCs and Alterations in Cardiovascular Physiology: Detroit Exposure and Aerosol Research Study (DEARS)

Hwashin H. Shin[a,b], Paul Jones[c], Robert Brook[d], Rob Bard[d], Karen Oliver[c], Ron Williams[c,*].

[a]Environmental Health Science and Research Bureau, Health Canada, Ottawa, Ontario, Canada

[b]Department of Mathematics and Statistics, Queen's University, Kingston, Ontario, Canada

[c]U.S. Environmental Protection Agency, Research Triangle Park, North Carolina, USA

[d]Division of Cardiovascular Medicine, University of Michigan, Ann Arbor, Michigan, USA

*Corresponding author

US Environmental Protection Agency, MD E-205-04,

Research Triangle Park, NC 27711, USA.

Tel: 1 919 541 2957.

Fax: 1 919 541 0905.

E-mail: williams.ronald@epa.gov

Journal: Atmospheric Environment

List of Abbreviations

DEARS, Detroit Exposure Aerosol Research Study
EPA, Environmental Protection Agency
CV, cardiovascular
ETS, environmental tobacco smoke
SBP, systolic blood pressure
DBP, diastolic blood pressure
HR, heart rate
BAD, brachial artery diameter
FMD, flow mediated dilatation
NMD, nitroglycerin mediated dilatation
VOC, volatile organic compound
PCA, principal component analysis
PC, principal component
$PM_{2.5,}$ Fine particulate matter
NO_2, nitrogen dioxide
BMI, body mass index
FDR, false discovery rate

Abstract

Background: An adult cohort consisting of 63 participants engaged in the US EPA's recent Detroit Exposure and Aerosol Research Study (DEARS) and a University of Michigan cardiovascular sub-study conducted during summer and winter periods over 3 years between 2004 and 2007 (5 seasons in total). Through all participants' wearing of a monitoring vest, personal exposures to various air pollutants were measured.

Purpose: The study objective was to identify the association between personal exposure to volatile organic compounds (VOCs) and six cardiovascular health endpoints in an adult non-smoking cohort of the DEARS.

Methods: Twenty five VOCs were collected using the DEARS exposure vest incorporating advanced passive diffusion tube. Six cardiovascular health endpoints including systolic and diastolic blood pressure (SBP, DBP), heart rate (HR), brachial artery diameter (BAD), brachial artery flow-mediated dilatation (FMD) and nitroglycerin-mediated arterial dilatation (NMD) were collected by novel, in-home clinical examinations. To reduce the number of personal VOCs highly correlated to each other, a principal component analysis was conducted. Accounting for more individual variations in association between personal VOCs and cardiovascular health endpoints, a linear mixed model was employed, where cohort subjects were not necessarily to have the same linear association.

Results: Applying the principal component analysis, 3 out of 12 components were retained, which appeared to involve a petroleum source (1st component), a 1-3 butadiene source (2nd component), and an ambient (Freon) source (3rd component). Petroleum related VOCs were associated with increases in FMD and showed mixed relationships with NMD (lag 0-1 day increased NMD, lag 2 days decreased NMD). Butadiene related VOCs decreased DBP but increased HR and BAD. Freon (ambient background) related VOCs increased HR.

Conclusions: We observed mixed and variable results in this first study to evaluate the relationships between personal exposures to VOCs of different origin on cardiovascular physiology. In sum, the findings suggest that VOCs may have rapid impacts upon the human cardiovascular system; however, understanding the health implications and the mechanisms responsible is beyond the scope of this investigation.

Keywords: cardiovascular, exposure assessment, volatile organic compounds, principal component analysis, DEARS, linear mixed model

1. Introduction

The Detroit Exposure and Aerosol Research Study (DEARS) has proven to be a tremendous resource in defining critical spatial and temporal variability of particulate matter, criteria gas pollutants, volatile organic compounds (VOCs), and other important pollutants at the personal, residential and ambient spatial settings (Stevens et al., 2014; Hammond et al., 2013; Bereznicki et al., 2012; Williams et al., 2012; Duval et al., 2012; Williams et al., 2012a; George et al., 2011; Brook et al., 2011a). Collecting nearly 36,000 individual (24-hr) based exposure measures, its depth has provided the ability to critically examine how humans are exposed to various pollutants and, in many situations, the impact of these exposure sources upon observable health effects. In particular, DEARS findings have revealed the highly variable nature of $PM_{2.5}$ and criteria gas (O_3, SO_2, NO_2) species across spatial settings and in some instances defined source impacts upon cardiovascular-related health outcomes (Brook et al., 2011b; Rodes et al., 2010; Williams et al., 2009).

Many studies have concluded that personal exposures may not be adequately represented by ambient or outdoor measures of VOCs (Stocco et al., 2008; Sexton et al., 2004a, b; Adgate et al., 2004). DEARS participants had the potential to be exposed to numerous VOCs and VOC sources. As we have reported elsewhere (Bereznicki et al., 2013), numerous VOC sources at the ambient setting would appear to exist in the Detroit metropolitan area. The current report defines the personal exposure of DEARS participants to 25 common VOCs, their potential sources, and resulting health outcomes linked to these exposures. To our knowledge, this effort represents the most extensive examination of these inter-related issues involving non-occupational exposures in the scientific literature.

The study objective was to identify the association between personal exposure to VOCs and cardiovascular (CV) health outcomes in an adult non-smoking cohort of the DEARS. Six CV health endpoints such as systolic and diastolic blood pressure (SBP, DBP), heart rate (HR), brachial artery diameter (BAD), brachial artery flow-mediated dilatation (FMD) and nitroglycerin-mediated arterial dilatation (NMD) were collected by novel, in-home clinical examinations.

Section 2 describes data collection method and process of the 25 personal VOCs, 6 cardiovascular health outcomes, and demographic and medical background of the participants. In Section 3, we discuss statistical approaches with standardizing VOCs, principal component

analysis, and liner mixed models. Results from the models are reported and compared for each CV health outcome in Section 4 followed by discussions and conclusions in Section 5 and 6, respectively.

2. Data and Materials

All participants were pledged to be non-smokers living in a non-smoking household, at least 18 years old and capable of following the study protocol. Informed consent was obtained prior to all participation activities. A summary of participant recruitment activities and their respective characteristics have been previously defined (Phillips et al., 2010). The main DEARS protocol has been reported in depth (Williams et al., 2009) and supporting information is available at the study's website (www.epa.gov/dears). To avoid any unexpected biases, we collected data with no exclusion criteria for race, gender, occupation, medications, or health status. VOC data at community (ambient) and residential (outdoor through site monitoring devices) levels were collected, which occurred within 6 Detroit area neighborhoods during summer and winter periods over 3 years between 2004 and 2007 (total 6 seasons).

DEARS exposure study participants were invited also to participate in the CV sub-study while it was occurring (during seasons 2-6). Note that the VOC data were available for all seasons 1-6, whereas the CV data were for seasons 2-6. The study results are therefore based on 5 seasons. Overall, most subjects participated in 3-5 study days in total (not necessarily in consecutive days, but all within the same week), and the number of participants for the number of study days by season is summarized in Table 1.

Table 1: Number of participants for total study days by season

	Number of participants				
	2005	2006		2007	
	winter	summer	winter	summer	winter
Number of study days (per season)	season 2	season 3	season 4	season 5	season 6
5	2	5	13	18	7
4	2	8	5	5	4

3	4		3	1	2
2	1			1	

144

145 **2.1 Personal VOC Exposure Assessments**

146 While both ambient and outdoor VOC measurements were also collected in the DEARS, our
147 focus here is on reporting personal VOC exposures involving 24-hour based monitoring periods
148 obtained from participants associated with season 2 (2005 winter) through season 6 (2007
149 winter). Personal VOC monitors were fixed in the breathing zone on nylon exposure vests
150 which the participants wore at all times except during periods of napping, bathing or night sleep.
151 Samples for VOCs analyses were collected passively using stainless steel diffusion tubes
152 containing Carbopack X (40/60 mesh, Supelco, Bellefonte, PA) and then thermally desorbed
153 and analyzed by GC-MS as described elsewhere (McClenny et al., 2005a, 2005b). Additional
154 information on the collection and analysis of VOC samples have been reported in depth
155 elsewhere (George et al. 2011; Bereznicki et al., 2012; Johnson et al, 2010).

156

157 Each sample had a 24 (+/- 2 hour) duration period and were obtained on a Tuesday through
158 Saturday schedule. Representative field and laboratory blanks as well as field and laboratory
159 controls were utilized during the DEARS to allow for careful determination of VOC levels as
160 defined in the Study Design (www.epa.gov/dears). A total of 25 VOCs were examined in the
161 study and included common species such as benzene, toluene and freon 113 among others.
162 Ultimately, and as defined in Section 3, a smaller number of VOCs (12) were incorporated into
163 the final statistical analysis based on data availability.

164

165 We have previously reported upon the impact of protocol compliance in the determination of
166 true personal exposure monitoring (the wearing of personal exposure monitoring devices as
167 defined by the study design) in both Rodes et al. (2010) and Lawless et al. (2012). In particular
168 we defined personal monitoring compliance here with the adherence of wearing the monitoring
169 vest a minimum of 60% of non-sleep hours and being exposed to a maximum of 1.5 $\mu g/m^3$ of
170 $PM_{2.5}$-related environmental tobacco smoke (ETS) during each 24 hour period. A total of four
171 non-exclusive, participant categories have been distinguished in the DEARS relative to the
172 protocol compliance and ETS exposure characteristics, (Williams et al., 2012b). These include
173 an “all-subject” category where no censoring of data relative to their ETS exposure or full
174 compliance in wearing the monitoring vest took place. The “vest” category is a subgroup
175 indicative of participants who fully complied with wearing the vest and therefore their data is

expected to be a good measure of true "personal" exposure. The "low" subgroup represents participants who had low ETS exposure but might not have fully complied with wearing the monitoring vest as requested. The final category, "vest-low" represents data for participants who both fully complied and had very low levels of ETS. ETS was an important consideration as it is a potential source of many air pollutants, including VOCs. Of the full subject population, overall the distribution of the total sampling population falling within the four categories (all-subject; vest; low; vest-low) were 100%, 70%, 60%, and 40%, respectively. Data findings associated with all four participant groups are presented in this report relative to observable health outcomes (Table 7).

2.2 Cardiovascular Endpoint Assessments

In parallel with the personal VOC sampling, CV study visits were performed at the participant's home for up to 5 consecutive evenings, Tuesday through Saturday, between 4 and 7 PM as previously defined (Brook et al., 2011a,b). These visits took place on concurrent days while subjects wore the vest monitors. There were 6 CV outcomes: blood pressure (SBP and DBP), heart beat (HR), indicative of basal arterial tone (BAD), indicative of endothelial-dependent vasodilatation (FMD), and indicative of non-endothelial dependent vasodilatation including smooth muscle function (NMD). Details regarding the methods involved in determining the health outcomes are described in prior manuscripts (Brook et al., 2011a).

Volunteers crossing over into the CV study underwent an additional visit at which time written informed consent was obtained and the average of the 2nd and 3rd of three seated blood pressure measurements using an automated oscillometric device as previously described (Brook et al., 2011a) was determined along with a fasting lipid profile and glucose (Cholestech LDX analyzer, Cholestech Corp).

There were originally 65 participants in this study, but two volunteers participated only one day. Since at least two daily observations per subject were required for our analysis, those two subjects were excluded. Of a total of 63 participants over the study period of five seasons, who provided the 6 CV outcomes, 18 subjects participated two seasons of summer and winter. Considering the time interval between two seasons, we considered those subjects separated, which resulted in 81 subjects with 355 observations in total. George et al. (2011) clearly show that seasonality plays a critical role in the exposure pattern of the DEARS participants to select

VOCs (e.g. benzene). In particular, Figure 3 of that reference depicts the often multi-fold difference in personal exposure as a function of seasonality. Not only do we see a high degree of variability of VOC in the outdoor environment as a function of season, but personal exposure and human exposure factors (e.g., household ventilation practices such as opening windows in the summertime versus closed windows in the winter) help drive the different seasonality traits observed for the DEARS participants. Therefore, personal exposure patterns as well as other exposure factors help drive the independent nature of the participants' exposure. Overall, the six CV outcomes had relatively high completions except for NMD: SBP, DBP and HR had completion of 99%, BAD of 90%, FMD of 82%; NMD had a low completion of 46% due to many subjects declining to take sublingual nitroglycerin which is required for this protocol.

2.3 Demographic and medical background information

Upon enrollment into the heath outcome sub-study of DEARS, we performed a screening evaluation which included a brief history and physical exam, as well as the signing of a written informed consent document approved by the University of Michigan Institutional Review Board. Subjects reported to the study investigators demographic details (age, sex, race, health status information including presence of cardiovascular diseases or risk factors, and current medications). Height and weight were measured as previously described (Brook et al., 2011a).

Of the 63 participants the average age was 45 from a range between 19 and 80 with more female (78%) than male (22%). For race, most of the participants were either African-American (55%) or Caucasian (43%). Indicating the participants' overall health status, the average BMI was 31, and 27% of the participants reported taking 1 or more heart related medication as described previously (Brook et al., 2011a). A basic statistics of each CV health endpoint is summarized in Table 2.

Table 2. Subject Characteristics

Factor	N	Mean or %	SD	Minimum	Median	Maximum
Age (years)	63	45	14.7	19	44	80
Gender	63					
Female	49	78%				
Male	14	22%				

Race	63					
African American	35	55%				
Caucasian	27	43%				
American Indian	1	2%				
Body Mass Index	61	30.7	7.6	16.7	29.5	56.5
Medicine usage	63					
yes	17	27%				
no	46	73%				
Cardiovascular						
SBP (mm Hg)	350	126.6	18.2	91.0	124.0	205.0
DBP (mm Hg)	350	75.1	10.0	50.0	75.0	101.0
HR (beats/min)	349	74.3	11.0	50.0	74.0	103.0
BAD (mm)	318	4.0	0.8	2.1	4.0	6.5
FMD (%)	290	3.2	5.2	-12.2	2.9	19.7
NMD (%)	164	14.7	7.2	-6.6	14.2	36.9

3. Methods

3.1 Missing data

Overall, the pattern of missing samples increased for the 4th and 5th visit (Table 3), which is expected due to the availability of participants during weekend periods where personal schedule were less predictable. In general, participation in any monitoring event begins to decrease as the study progresses (participant fatigue). Since, at most, five personal VOC observations were available for each subject, imputations were not attempted. Excluding all missing data, the total number of daily observations was reduced from 355 to 239. For each sample, there were 25 species of personal VOCs analyzed and, based on data availability, we screened out those which had less than 75% availability over the whole study period. This resulted in 12 personal VOCs with data availability ranged 78%-88%, which indicates there were 12%-22% of missing data for those selected personal VOCs.

Table 3: Data availability by study day (day 1 to 5)

Study day	Availability (%)
1	24

2	23
3	22
4	18
5	13
Total	100

252

253 **3.2 Standardized VOCs**

254 Each VOC has different distribution as summarized in Table 4. Even if the unit of measurement
255 of the VOCs is the same in parts per billion by volume (μg/m^3), all VOCs were standardized to
256 have mean zero and standard deviation 1. This is helpful to work with standardized regression
257 coefficients in comparing the associations between personal VOCs and CV health outcomes,
258 which will be discussed in later section.

259

260 Table 4: Descriptive statistics of 12 personal VOCs (unit: μg/m^3)

VOC* (N=239)	mean	SD	min	Q1**	median	Q3**	max
PBENZ (benzene)	5.21	5.52	0.76	2.39	3.68	5.90	56.93
PBUDI (1,3 butadiene)	1.38	1.46	0.13	0.66	0.99	1.55	14.82
PBZ13 (1,3,5-trimethylbenzene)	1.92	2.89	0.36	0.86	1.21	1.95	38.58
PETBZ (ethylbenzene)	3.90	7.29	0.60	1.36	2.29	3.67	76.09
PF113 (freon 113)	0.81	0.26	0.37	0.65	0.71	0.88	1.45
PMPXY (meta, paraxylene)	11.84	22.16	1.72	4.01	7.27	11.55	264.81
POXYL (orthoxylene)	4.18	8.68	0.61	1.39	2.44	3.81	97.20
PPDCL (paradichlorobenzene)	19.01	48.19	0.19	1.05	1.75	5.05	357.04
PPERC (perchloroethylene)	2.89	9.69	0.19	0.55	0.79	1.40	125.49
PPETO (para ethyl toluene)	1.38	2.00	0.21	0.57	0.89	1.38	25.24
PSTYR (styrene)	1.86	1.59	0.35	0.84	1.33	2.10	9.57
PTOLU (toluene)	19.33	17.57	3.01	8.75	14.02	23.26	108.42

261 *The first letter of each VOC's name ("P") stands for personal exposure.

262 **Q1 and Q3 represent the 25% and 75% percentile, respectively.

263

264

265 **3.3 Principal Component Analysis**

266 To examine the relationships among the 12 personal VOCs, we first looked at their pairwise
267 correlations (Pearson). Five out of 12 VOCs had very high correlations up to 0.98-0.99, and this

implies that not all five of those VOCs would be necessary to estimate the associations between VOCs and CV health endpoints.

To reduce the number of personal VOCs, we employed Principal Component (PC) analysis. Since there are 12 personal VOCs (original data), there are also 12 PCs (new data), which are linear combinations of weighted VOCs. The weights (called loadings) are optimized representing the correlation between the VOCs and PCs. We examine the weights and then determine what PCs would be retained based on the following three criteria among various rules of thumb proposed to date (Fekedulegn et al., 2002; Hair et al., 2005):

- Eigenvalue-one criterion
- Proportion of variance accounted for
- Interpretability

The eigenvalue is a measure of how much of the variation of the 12 personal VOCs (total variance) each component explains. We include components, whose eigenvalues are larger than or close to 1, accounting for at least **10%** of the total variance. The total number of PCs retained would be determined where the cumulative percent of variance accounted for at least **70%** of the total variance. The interpretability criterion requires that each PC should contribute with relatively high loadings (typically **40%**) on only one PC and near zero loadings on the other PCs.

There were four eigenvalues in order 5.87, 1.45, 1.37, and 0.98, which were larger than or close to 1. When using 4 PCs corresponding to these four eigenvalues, 81% of total variance was explained. However, one VOC (PF113) violated the criterion on interpretability that each VOC should contribute to one particular PC as it contributed to two PCs over 40%. We thus decided to retain the first three PCs, by which 72% of total variance was explained, and none the criteria discussed above were violated.

3.4 Linear Mixed Model

The participants of the DEARS cohort were assumed to be randomly selected from the target population of pre-selected neighborhoods as described in more detail elsewhere (Williams, 2005; Brook et al., 2011b; Williams et al., 2012). Within subject, the associations between each of the CV health outcomes (response) and personal exposure to VOCs (predictors) appeared to be linear overall. For these linear associations, which are characterized by intercept and slope,

we allowed the intercept to vary at random over individuals but the slope to be fixed (the same for all individuals). Since data were collected over time (study days) on the same participants, we considered a linear mixed model combining fixed effects and random effects (Brady, et al. 2007; Mohamed, et al., 2007). Note that the 12 personal VOCs (original data) were then transformed into a few PCs retained (new data) as discussed in earlier section.

The linear mixed model for our analysis on the VOC-CV association includes effect modifiers and confounders: demographic factor (age, gender, race), medical background factor (body mass index, cardio-related medicine usage), and environmental factor (ambient temperature, personal $PM_{2.5}$, personal Nicotine, and personal NO_2). The relationship between these factors and CV responses is assumed to be common to all subjects. In equation,

$$Y_{ij} = \beta_0 + \beta_1 VOC_{PCi} + \beta_2 D_i + \beta_3 M_{ij} + \beta_4 E_i + \alpha_i + \varepsilon_{ij} \quad (1)$$

where Y_{ij} is the CV response for subject *i* at study day *j,* VOC_{PCi} the principal components of the personal VOCs, D_i the demographic variables, M_i medical background variables and E_i the environmental variables. The base model (1) includes fixed effects associated with the subject-level covariates (β's), a random effect associated with the intercept for each subject (α_i) and a residual associated with each observation (ε_{ij}). The random effects by subject were assumed to be independently distributed across subjects with a normal distribution $\alpha_i \sim N(0, \delta^2)$. The within-subjects errors ε_{ij} were assumed to be distributed $\varepsilon_{ij} \sim N(0, \sigma^2 R_i)$, where R_i is the variance-covariance matrix for the residuals. It is also assumed α_i and ε_{ij} are independent of each other. The first-order autoregressive structure, denoted by AR(1), was explored for the covariance R_i in the analysis, which implies observations closer to each other in time exhibit higher correlation than observations farther apart in time.

3.5 Participants grouping and Base model

As stated earlier, all participants were supposed to be non-smokers living in a non-smoking household wearing the vest all the time during the study period. In practice, however, this requirement was not always satisfied. We classified all participants into four groups by vest compliance and exposure to nicotine to account for potential second-hand smoking (or ETS): all-subject group, vest group (vest compliance ≥ 60%), low group (Nicotine ≤ 1.5 μg/m^3), and vest-low group (vest compliance ≥ 60% and Nicotine ≤ 1.5 μg/m^3). The vest compliance was

mathematically determined by examination of the electronic signature of the personal exposure monitoring device relative to key parameters including sensor temperature (proximity to the human body) and 3-D sensor movement (accelerometry) as defined in Lawless et al. (2012).

For each group we conducted a sensitivity analysis by lag of personal air pollutants (lag 0 & 1 day of $PM_{2.5}$, Nicotine, NO_2) and personal VOCs (lag 0,1 & 2 days). Note that only one lag of the VOCs was considered in each model (Table 5). Since the effect of ambient temperature (Temp) is known immediate, no lag was considered for temperature. The base model (Model A) can be simply written as follows:

$$CV \sim PC1 + PC2 + PC3 + PM_{2.5} + Nicotine + NO_2 + Age + Gender + Race + BMI + Medicine + Temp, \quad (2)$$

where the PCs are the three principal components retained, and $PM_{2.5}$, Nicotine, and NO_2 the personal air pollutant concentrations (AP) in consideration. As summarized in Table 5, there were five more models in addition to the base model. Note that all the six models were applied to the four groups, respectively, and this implies that the influence by the effect modifiers and confounders mentioned in previous section varies over the four groups. For example, the effect of $PM_{2.5}$ on the CV health endpoints is not necessarily the same for all groups.

Table 5: Six models by lags of air pollutants and VOCs

	AP Lag 0	AP Lag 1
VOC Lag 0	Model_A (base model)	Model_B
VOC Lag 1	Model_C	Model_D
VOC Lag 2	Model_E	Model_F

3.6 Unadjusted and adjusted p-values for multiple health endpoints

The p-value has been used for the strength of the significant association as well as testing significance. In this study, we report the p-values with more weight on the former than the latter. As we compared the 6 CV multiple endpoints for the same subjects (in group), VOC exposure and all other confounders including effect modifiers using model (2) above, there existed potential erroneous false positive outcomes (Benjamini and Yekutieli, 2001). To address this

concern, the false discovery rate (FDR), suggested by Benjamini and Hochberg (1995) as the expected proportion of erroneous rejections amongst all rejections, was employed. Benjamini and Yekutieli (2001) offer further rigorous discussions on the FDR methods. To maintain the balance between erroneous rejections and low detection power in multiple comparisons, we report both unadjusted p-values avoiding a potential over-adjustment and adjusted p-values controlling the FDR.

4. Results

4.1 Source of personal VOCs

Applying the PC selection criteria, three PCs were retained: the 1st component, PC1, found in common among 7 VOCs (BENZENE, PBZ13, PETBZ, PMPXY, ORTHOXYLENE, PPETO, TOLUENE in Table 6) seems to measure **a primary petroleum source**; the 2nd component, PC2, among three VOCs (PBUDI, PPERC, STYRENE) seems to measure **a butadiene source** from industrial emissions; the 3rd component, PC3, between two VOCs (PF113, PPDCL) seems to measure **freon and industry source** from Freon and industrial solvent (Table 6). Since Freon 113 exists in nearly consistent levels in the lower atmosphere, this component is believed to be a more general (background) source to which some localized source (personal PDCL) is also present. Bereznicki et al (2013) observed a localized outdoor PDCL source in a number of the DEARS neighborhoods, but we were unable to fully isolate its primary point(s) of origin. Even so, it must be acknowledged that indoor sources of PDCL are known to exist and could have played a role in this principal component

Among the 12 personal VOCs, only PPERC was not explained adequately by the three PCs, whereas the other 11 VOCs were explained well (Table 6). PPERC is a common dry cleaning solvent, and personal exposures to this VOC might have been influenced by the presence of recently laundered clothes in the participant's residence but on such an inconsistent basis that a lack of statistical power existed to fully distinguish this component successfully.

Table 6: Standardized loadings and communality from three retained PCs

VOC*	PC1**	PC2**	PC3**	Communality***
PBENZ (benzene)	**0.87**	0.05	-0.09	77%

PBUDI (1,3 butadiene)	0.09	**0.76**	-0.13	61%
PBZ13 (1,3,5-trimethylbenzene)	**0.93**	0.00	-0.11	87%
PETBZ (ethylbenzene)	**0.88**	0.20	0.21	86%
PF113 (freon 113)	0.11	-0.30	**0.67**	55%
PMPXY (meta, paraxylene)	**0.94**	0.13	0.15	92%
POXYL (orthoxylene)	**0.89**	0.16	0.21	86%
PPDCL (paradichlorobenzene)	0.01	0.17	**0.88**	80%
PPERC (perchloroethylene)	0.00	**0.48**	-0.04	23%
PPETO (para ethyl toluene)	**0.93**	0.01	-0.06	86%
PSTYR (styrene)	0.31	**0.77**	0.20	73%
PTOLU (toluene)	**0.77**	0.15	0.14	63%

*The first letter of each VOC's name ("P") stands for personal exposure.

**Rotated PCs

***Communality indicates the portion of each VOC explained by the three PCs included. For example, 77% of the variance in BENZENE was explained by the three PCs.

4.2 Association between Cardiovascular disease and personal VOCs

Table 7 displays CV risk estimates in terms of PCs, not the original personal VOCs. This is desirable for two reasons. First, we are interested in the source of the VOCs rather than the VOC itself. Second, the association between personal VOCs and CV health outcomes becomes more consistent when using PCs instead of the individual VOCs. As a result, we focus on the association (positive or negative versus none) avoiding typical interpretation in terms of the change in CV health outcomes by the unit change in the PCs.

SBP was unique among the six CV health outcomes that it was not associated with any three PCs, whereas the other five CVs were consistently related to some PCs.

DBP was strongly associated in negative way with PC2 only, which is a butadiene source (Table 7). In other words, the butadiene source VOCs lowered DBPconsistently over all the four groups. The significant associations were observed for VOCs lagged by 0 or 1 day but not for 2 days. This implies that the impact of butadiene related VOCs on DBP is overall immediate within a day since exposure.

Heart rate was increased by PC2, butadiene related VOCs, for all groups except for the all-subject group (Table 7). The consistency among the three groups, which were more refined groups than the all-subject group, supports this association between butadiene related VOCs and Heart rate. Heart rate was also increased by PC3, Freon and industry related VOCs, over all the four groups. It is noticed that both associations were significant for the VOCs lagged 2 days but not lag 0 or 1 day. This may suggest that the impact of butadiene related VOCs and Freon and industry related VOCs on heart rate is not immediate but delayed by a couple of days. Note that there is no correlation between butadiene related VOCs and Freon and industry related VOCs, since they were characterized by the principal component analysis. This implies that heart rate is clearly affected by both butadiene related VOCs and Freon and industry-related VOCs.

Table 7: DBP and heart rate associated with PCs

CV health outcome	Model[1]	Group[2]	PC[3]	N[4]	Association estimate[5]	SE (Association estimate)	p-value[6]
DBP	B	all-subject	PC2	157	-25.368	10.591	0.019
	B	low	PC2	102	-24.397	11.417	0.037
	B	vest-low	PC2	70	-24.490	11.406	0.039
	C	vest-low	PC2	65	-33.295	10.800	0.004
	C	vest	PC2	111	-27.858	10.414	0.010
	C	low	PC2	94	-29.408	11.083	0.011
	D	all-subject	PC2	162	-21.536	10.585	0.045
	D	vest	PC2	109	-30.317	11.137	0.008
	D	low	PC2	100	-27.011	10.865	0.016
	D	vest-low	PC2	68	-31.470	10.715	0.006
Heart Rate	E	vest	PC2	81	30.307	14.782	0.048
	E	vest	PC3	81	34.663	16.555	0.043
	E	low	PC2	72	32.445	14.474	0.034
	E	low	PC3	72	38.541	17.773	0.039
	E	vest-low	PC2	52	41.237	15.068	0.014
	E	vest-low	PC3	52	45.961	20.306	0.037

	F	all-subject	PC3	122	31.380	14.721	0.037
	F	vest	PC2	85	28.679	13.847	0.045
	F	vest	PC3	85	45.465	15.870	0.007
	F	low	PC3	77	52.889	18.167	0.007
	F	vest-low	PC1	56	12.735	5.683	0.037
	F	vest-low	PC2	56	38.848	16.256	0.027
	F	vest-low	PC3	56	60.324	22.232	0.013

[1]Models by lag of VOCs and air pollutants in Table 5 (section 3.5). A is the base model with VOC and confounder AP on the same day as the health outcomes observed; B is with VOC on the same day and AP lag 1-day; C is with VOC lag 1-day and AP on the same day; D is with both VOC and AP lag 1-day; E is with VOC lag 2-day and AP on the same day; F is with VOC lag 2-day and AP lag 1-day.

[2]Four groups defined in section 3.5

[3]PC1= 1st principal component for Petroleum related VOCs; PC2= 2nd principal component for Butadiene related VOCs; PC3=3rd principal component for Freon & industry related VOCs (section 4.1)

[4]Number of observations in the model.

[5]The impact of VOC on CV health outcome: change of DBP in mm Hg per unit μg/m^3 PC: change of Heart Rate in beats/min per unit μg/m^3 PC. (Here unit change in PC means a change of standard deviation of each VOC included for that PC.)

[6] Statistical significance was defined as $p<0.05$.

FMD was consistently increased by PC1, petroleum related VOCs, for all groups (Table 8). Note that the association is significant only for VOCs with no lag. This may suggest the impact of the petroleum related VOCs on FMD was immediate as observed on the same day. The extent of association also seems to be related to the lag of the air pollutants included in the model: the association became lower with the air pollutants lag 1 day than no lag.

BAD was associated with all three PCs, but consistently with PC2 only (Table 8). It was increased by PC2, butadiene related VOCs, over the four groups all. Like heart rate, the butadiene related VOCs lagged 2 days increased BAD.

NMD was associated with PC1, petroleum related VOCs, for all four groups but in different ways according to the lag of the VOCs (Table 8). The petroleum related VOCs lagged 0-1 day

increased NMD, whereas the VOCslagged 2 days decreased NMD. Note that the negative associations were estimated from relatively smaller number of observations and thus further investigation with more observations is necessary to better understand the association between petroleum related VOCs and NMD.Table 8: FMD, BAD, and NMD associated with PCs

CV health outcome	Model[1]	Group[2]	PC[3]	N[4]	Association estimate[5]	SE (Association estimate)	p-value[6]
FMD	A	all-subject	PC1	179	6.316	2.362	0.009
	A	vest	PC1	116	7.371	2.637	0.007
	A	low	PC1	86	7.725	2.692	0.006
	A	vest-low	PC1	58	7.620	3.163	0.023
	B	all-subject	PC1	139	6.360	2.382	0.009
	B	vest	PC1	90	7.315	2.675	0.009
	B	low	PC1	94	6.724	2.517	0.010
	B	vest-low	PC1	63	6.915	2.939	0.025
BAD	B	vest	PC3	93	-1.627	0.801	0.047
	E	all-subject	PC2	108	1.096	0.538	0.047
	E	vest	PC2	72	1.351	0.628	0.040
	E	low	PC2	68	1.440	0.598	0.025
	E	vest-low	PC2	48	1.558	0.615	0.025
	F	all-subject	PC1	113	0.305	0.149	0.047
	F	all-subject	PC2	113	1.277	0.463	0.008
	F	vest	PC2	76	1.517	0.598	0.017
	F	low	PC2	73	1.302	0.605	0.041
	F	vest-low	PC2	52	1.592	0.630	0.023
NMD	A	low	PC1	52	18.026	7.378	0.023
	B	all-subject	PC1	79	13.124	6.433	0.048
	C	all-subject	PC1	80	14.576	5.749	0.015
	C	low	PC1	50	19.172	8.951	0.045
	E	all-subject	PC1	58	-20.010	6.669	0.006
	E	vest	PC1	35	-20.048	8.024	0.032
	E	low	PC1	39	-20.944	8.938	0.037

	E	vest-low	PC1	26	-29.542	11.013	0.044
	F	all-subject	PC1	61	-16.484	7.196	0.031
	F	vest	PC1	39	-18.782	7.541	0.028
	F	vest-low	PC1	29	-33.593	9.957	0.012

[1]Models by lag of VOCs and air pollutants in Table 5 (section 3.5). A is the base model with VOC and confounder AP on the same day as the health outcomes observed; B is with VOC on the same day and AP lag 1-day; C is with VOC lag 1-day and AP on the same day; D is with both VOC and AP lag 1-day; E is with VOC lag 2-day and AP on the same day; F is with VOC lag 2-day and AP lag 1-day

[2]Four groups defined in section 3.5

[3]PC1= 1st principal component for Petroleum related VOCs; PC2= 2nd principal component for Butadiene related VOCs; PC3=3rd principal component for Freon & industry related VOCs (section 4.1)

[4]Number of observations in the model.

[5]The impact of VOC on CV health outcome: change of FMD or NMD in % per unit μg/m^3 PC; change of BAD in mm per unit μg/m^3 PC. (Here unit change in PC means a change of standard deviation of each VOC included for that PC.)

[6] Statistical significance was defined as $p<0.05$.

Note: All other insignificant results are available upon request, and the analysis was performed by function “lme (linear mixed-effects model)” in R (version 2.15.2).

The significant associations in Tables 7 and 8 are visualized with confidence intervals by the PCs in Figures 1 and 2.

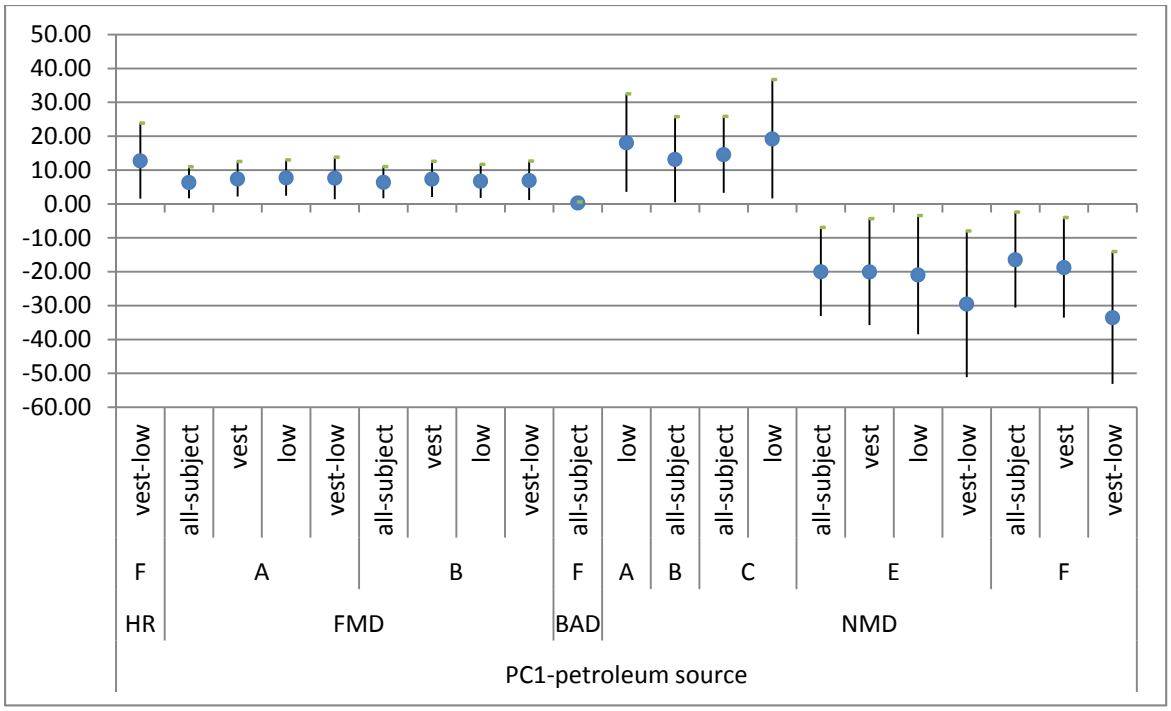

Figure1: 95% confidence intervals of the significant associations between PC1 and health outcomes.

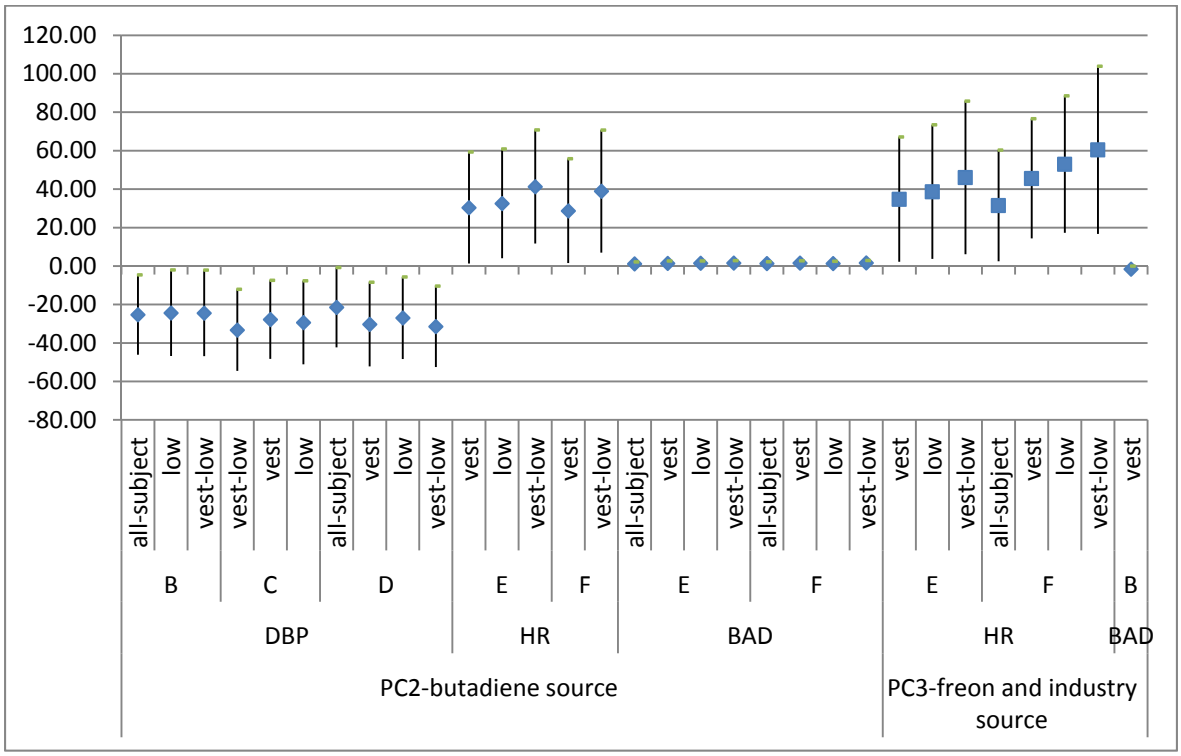

Figure2: 95% confidence intervals of the significant associations between PC2 or PC3 and health outcomes.

In addition to the unadjusted p-values reported in Tables 7 and 8, the adjusted p-values controlling the false discovery rate (FDR) are summarized in Table 9.

Table 9: Five CV health outcomes associated with PCs based on adjusted p-values

CV health outcome	Model[1]	Group[2]	PC[3]	N[4]	Association estimate[5]	SE (Association estimate)	p-value[6]
DBP	C	vest-low	PC2	65	-33.295	10.800	0.026
	D	vest-low	PC2	68	-31.470	10.715	0.035
Heart rate	F	vest	PC3	85	45.465	15.870	0.041
	F	low	PC3	77	52.889	18.167	0.041
FMD	A	vest	PC1	116	7.371	2.637	0.040
	A	low	PC1	86	7.725	2.692	0.039
BAD	F	all-subject	PC2	113	1.277	0.463	0.049
NMD	E	all-subject	PC1	58	-20.010	6.669	0.037

[1]Models by lag of VOCs and air pollutants in Table 5 (section 3.5). A is the base model with VOC and confounder AP on the same day as the health outcomes observed; B is with VOC on the same day and AP lag 1-day; C is with VOC lag 1-day and AP on the same day; D is with both VOC and AP lag 1-day; E is with VOC lag 2-day and AP on the same day; F is with VOC lag 2-day and AP lag 1-day.

[2]Four groups defined in section 3.5

[3]PC1= 1st principal component for Petroleum related VOCs; PC2= 2nd principal component for Butadiene related VOCs; PC3=3rd principal component for Freon & industry related VOCs (section 4.1).

[4]Number of observations in the model.

[5]The impact of VOC on CV health outcome: change of DBP in mm Hg per unit μg/m^3 PC: change of Heart Rate in beats/min per unit μg/m^3 PC; change of FMD or NMD in % per unit μg/m^3 PC; change of BAD in mm per unit μg/m^3 PC. (Here unit change in PC means a change of standard deviation of each VOC included for that PC.)

[6] Adjusted p-values controlling the false discovery rate. Statistical significance was defined as $p<0.05$.

5. Discussion

Humans are exposed to VOCs from a multitude of potential sources originating from both indoor and outdoor sources. While few studies have attempted to define VOC personal exposures in a subject population (Weisel et al., 2005; Edwards et al., 2001; Sexton, 2004a, b; Wallace et al., 1985), with rare exception have they attempted to identify the source of the exposure due to the complexity of the effort (Kim et al., 2002). Even less reported is the attempt to define VOC source exposures in a non-occupational setting. The associations between VOC exposure source and health outcomes reported in this study represent one of the seminal articles on this subject matter. Even so, while our focus was upon cardiovascular outcomes due to the nature of the DEARS primary study hypotheses, it must be recognized that the findings we describe cannot be considered definitive as many alternative health outcome parameters were not examined.

The data do however clearly provide strong and compelling evidence that, for the DEARS participants, three primary VOC source categories existed that significantly influenced their exposures to a number of common air pollutants. These included some VOC source categories containing human carcinogens (PC1; e.g., benzene). The fact that a petroleum source was evident in the data is not surprising. Participants would have been exposed to this source in such activities as being in proximity to near road traffic, refueling engines, and emissions from many common household consumer products. PC2 was representative of industrial emissions and had a significant 1,3 butadiene signature. This VOC is a common industrial material used in the Detroit area and is also associated with automotive traffic pollution. Bereznicki et al (2013) has categorized the primary VOC sources impacting DEARS residential outdoor monitoring sites, and identified multiple industrial activities that might have been responsible for the linkage between this source category and the observed personal exposures. Lastly, a source category (PC3) dominated by Freon 113 and para-dichlorobenzene was evident. Freon 113 levels were very consistent across all of the residential and ambient monitoring episodes in the DEARS and routinely with <10% concentration variability. It is well understood that this particular halogenated VOC is well distributed in the atmosphere to the point it could be considered a marker of outdoor air infiltration into residential structures (contingent upon properly operating local residential air conditioning and refrigeration systems). As stated earlier, PPDCL was known to sometimes exist in high concentrations in residential outdoor samples in collected

during the DEARS (Berezinicki et al., 2013) and that these non-identified point sources were of a consistent basis to influence the principal component analysis performed here.

A potential issue with our data treatment is whether or not the two-season data from same subjects (the specific 18 subjects) can be treated as independent. Our rational for assuming independence is based on two things. First, it can be visually examined through a plot (not shown), which shows different exposure-response linear relationship for those subjects by season. Second, we did take account for the correlation within subject by season using the linear mixed model. The covariance structure employed in this study was AR(1), autoregressive, which assumes homogeneous variances and correlation declining over time (here in day). If we combine, for example, 10 data for some subject (5 measurements for each summer and winter), there is an incomparable gap between the 5^{th} & 6^{th} measurements. With these two reasons we treated them as independent.

We also note that the subjects did not all contribute data points consecutively and that some individuals contributed less than five days of data points. This might suggest unequal weighting among the subjects, which has the potential to introduce a bias in estimates. We included those subjects, who had at least 2-day data each season, which is the minimum number of data for linear association between VOC and CV health endpoints. The degree of bias by the unequal individual contribution is expected to be minimized through our model assuming a linear association. As stated in Table 1, the percentage of the subjects who had 4- or 5-day data points is about 85% (69/81). This indicates overall comparable contributions among the subjects in this study.

As stated earlier in the Methods section, we focused our analyses not on the individual VOC but rather on the VOC component category. Therefore, the impact of any one VOC upon the CV outcomes we examined cannot be defined. Even so, some clear distinction between health outcomes and VOC types can be discussed. It was interesting that no discernable affect upon SBP was linked with any of the PC categories. Given the limitations of the study and its observational nature, it is not clear why other vascular and hemodynamic parameters were associated with VOC categories but SBP was not. It is not possible to know with certainty if this represents a true biological result, meaning the VOCs did not impact SBP, or a lack of adequate statistical power given that this study was not designed to evaluate this specific association.

PC1, the Petroleum related VOCs, was found associated positively with FMD (an increase in flow mediated dilatation) but negatively with NMD (a decrease in nitroglycerin mediated dilatation). Note that the NMD data availability was relatively low to the other CV health endpoints, and thus the strong association between PC1 and NMD could be less reliable.

On the other hand, PC2, the grouping heavily influenced by 1,3 butadiene, was strongly associated with a decrease in DBP. This effect was immediate (lag 0) and diminished by lag day 2. Likewise, PC2 was shown here to be linked with a decrease in HR but only at the lag day 2 time point. This VOC is a suspected A2 carcinogen but at least one source indicates it also has reported BP and HR reduction associations (Agency for Toxic Substances & Disease Registry, 1992). It is interesting to note that anecdotal evidence of chronic exposures effects to this PC have been reported relative to both fatigue and loss of general well-being status (Snyder, 1987). Reduction in both HR and DBP would be consistent with both of those health outcomes. ETS is a known source of 1,3-butadiene. Even so, we accounted for ETS exposures in our health outcome models and therefore it is reasonable to suggest that the PC2 category in this study was most likely evidence of personal exposures to industrial and other sources of this VOC.

PC3 had by far the weakest impact upon health outcomes. We did observe some increase in HR with this VOC source category under some of the participants grouping scenarios. Even so, one might suggest that this category, best summarized as that relating to primarily background VOC levels (ambient), had an overall weak potential for impacting the CV health outcomes in general.

We have previously reported that personal-level exposures to fine particulate matter were associated with elevations in blood pressure and heart rate, and trends towards reductions BAD (i.e., arterial vasoconstriction) during the same time windows evaluated in this current report. This health outcome sub-study of DEARS was designed and powered to evaluate the impact of fine particles on cardiovascular physiology with the interpretation and potential mechanisms involved having been discussed previously (Brook et al., 2011a,b). Therefore, it is important to acknowledge that the current findings regarding VOC sources being linked with both positive and negative associations with physiological parameters may represent chance findings due to the *post hoc* nature of these multiple analyses.

On the other hand, we did observe some consistent results. We can only speculate at this point as to the mechanisms responsible if we accept that these reported changes are valid. However, it is plausible that these inhaled VOC pollutants may trigger perturbations in the functionality of the cardiovascular system via several pathways. These have been described in regards to particulate matter; nonetheless, these mechanisms may also apply to inhaled gaseous (e.g., NO_x, ozone) and VOC pollutants. These include acute autonomic imbalance through stimulation of pulmonary receptors (resulting in changes that favor either sympathetic or parasympathetic tone), systemic inflammation arising from the spill-over of cytokines and/or activated cells from local inflammatory responses in the pulmonary tissues, and, finally, the direct translocation of pollutants within the systemic circulation having a direct impact on remote cardiovascular tissues (Brook et al., 2010). Far fewer studies have evaluated the impact of gaseous or VOC pollutants on cardiovascular outcomes or biological changes. Our results suggest that the latter may indeed provoke observable responses in humans.

The sum changes observed in each outcome will reflect the integrated impact of all these 3 general pathways, as well as any potential compensatory biological responses. Given the overall findings, the most logical interpretations are as follows: We posit that PC2 may have triggered a direct arterial vasodilatation upon inhalation (i.e., increased BAD), with a subsequent reduction in DBP. In this scenario, it is likely that the increased heart rate reflected a compensatory baroreflex-mediated response to maintain cardiac output. The pathway whereby PC2 caused the vasodilation may be via direct actions upon the vasculature or by altering autonomic tone. The physiology behind the other changes is less evident. However, it is possible that PC3 triggered an increase in HR, likely via stimulation of the sympathetic nervous system in a manner that was not profound enough to also elicit elevations in blood pressure or changes in observable vascular tone. Heart rate changes are the most sensitive and observable autonomic changes and therefore this remains a plausible supposition. Finally, the changes linked to PC1 remain very difficult to interpret given the variable responses in FMD and NMD over time. More studies will be required to speculate upon the health implications and the biology involved. Nonetheless, these first of a kind observations do suggest that VOCs from several sources can elicit observable changes in the cardiovascular system within a few days of exposures.

One of the components of the DEARS research has been the effort to determine the impact (value) of subcategories of personal exposure monitoring (Brook et al., 2011b; Williams et al.,

2012; Hammond et al., 2013). In the data reported here, we subcategorized four distinctive participants groups relative to personal VOC exposures and select CV health outcomes. These ranged from participants fully complying with wearing their monitoring vests to those who might not have been as compliant as well as some various distinctions in ETS exposures. In a remarkable outcome of consistency, the association estimates for all CV health outcomes, models, groupings, and PCs were at their highest in the subcategory of participants who faithfully wore their monitoring vest and who had ETS exposure levels within the study's defined criteria (< 1.5 $\mu g/m^3$ per 24h hour). As an example of this finding, we observed a range of DBP outcomes estimates between -21.5 mm Hg per unit $\mu g/m^3$PC for the all-subject group (having the lowest component of compliance) and ETS exposures and a value of -31.5 mm Hg per unit $\mu g/m^3$ PC for the vest-low subgrouping (the most compliant with low ETS exposures) for the Model D, PC2 health outcomes. This represented a 47% increase in outcome response. Other comparisons of this nature can be developed. For instance, we see a range of 31.4 bpm per unit $\mu g/m^3$PC and 52.9 bpm per unit $\mu g/m^3$ PC when we compare HR outcome estimates for model F, PC3 (all-subject vs low ETS). This represents a 68% difference in outcome effect. It is clearly evident from this and the aforementioned DEARS references to similar comparisons, that ensuring participants are compliant with performing the personal exposure monitoring protocol is vital to ensuring data quality needed for health outcome determinations. Likewise, unless one is interested in primarily investigating ETS exposure for CV cause and effect, it is encouraged for potential study participants to be excluded who have high potential for such exposures. It is obvious that the data having the closest reality to the person's true exposure and with minimal ETS exposure (vest-low) provided us the greatest opportunity to observe health effects.

We note that the FDR adjustment gained more detection power comparing results reported in Tables 7 and 8 with those in Table 9. By controlling the FDR, we observed a drastic reduction in significance, from 52 to 8 significant cases (15%). The FDR adjustment is known to be very useful for equally and positively correlated health endpoints. The 6 CV health endpoints in this study could be assumed to be equally likely to correlate together as we have no prior knowledge or belief available on this subject matter. This correlation potential would mean the VOCs would not be assumed to be more associated with any particular health endpoints as compared to the others. However, the 6 CV health endpoints can be either positively or negatively associated with some VOCs. For example, some VOCs might have the potential to raise the heart rate while also lowering lower blood pressure in an individual. Such a possibility suggests a potential

over-adjustment in the FDR adjusted p-values if used without direct knowledge of the correlation structure of the pollutants and health outcomes. Since we do not know this for certain, the FDR adjusted p-values are provided here for informational purposes only with the primary discussion of results still associated with findings reported in Tables 7 and 8. To be conservative regarding the VOCs-CV associations, one may prefer unadjusted p-values to the FDR adjusted ones until the aforementioned correlation structure can be clearly identified.

6. Conclusions

The DEARS has reported observed CV health outcomes in an adult population associated with personal exposures to a wide range of air pollutants. These include $PM_{2.5}$ mass, $PM_{2.5}$ mass components, NO_2 and now VOCs. In this latest report, we specifically did not target any VOC directly but chose to categorize groupings of VOCs determined to correlate closely with other VOCs relative to personal exposure relationships. This approach provided the statistical methods, which not only secured a means to establish personal exposure health outcomes, but also provided insight on particular sources of that exposure. This is a fundamental issue that should be considered by others as they potentially consider repeating studies of this nature. The statistical power needed to truly differentiate the impact of closely related VOCs upon any single health outcome would be extremely hard to meet. Our findings clearly demonstrate that monitoring participants under close supervision and excluding participants with low wearing protocol compliance, who can cloud the ultimate statistical analyses, offers the greatest opportunity for securing adequate statistical power to conduct such epidemiological research involving a general population.

Acknowledgements

The US Environmental Protection Agency through its Office of Research and Development funded and conducted the research described here under contract 68-D-00-012 (RTI International), EP-D-04-068 (Battelle Columbus Laboratory), 68-D-00-206 and EP-05-D-065 (Alion Science and Technology). It has been subjected to Agency review and approved for publication. Mention of trade names or commercial products does not constitute endorsement or

recommendation for use. This study was also supported by the Electric Power Research Institute (Contract EP-P15887/C7915) and from a National Institutes of Health General Clinical Research Center Grant: M01-RR000042. Carry Croghan and Alan Vette (US EPA) assisted in exposure data tabulation. Herb Jacumin, Hunter Daughtrey, and Lydia Brouwer (Alion Science and Technology) are acknowledged for their assistance in VOC laboratory analyses. Charles Rodes and Jonathan Thornburg along with the field staff of RTI International were responsible for performing the field data collections involving the exposure measurements. The study was approved by Institutional Review Boards of the University of Michigan and RTI International as well as the Human Subjects Approving Official of the U.S. Environmental Protection Agency (EPA).

The authors also thank the two anonymous reviewers whose comments helped clarify important findings and improve the paper.

References

Adgate, J.L., Eberly, L.E., Stroebel, C., Pellizzari, E.D., Sexton, K. Personal, indoor, and outdoor VOC exposures in a probability sample of children. Journal of Exposure Analysis and Environmental Epidemiology 14 (Suppl 1), S4–S13 (2004).

Agency for Toxic Substances & Disease Registry.Toxicological Profile for 1,3 butadiene p.17 TP-91/07 (1992).

Benjamini, Y., Yekutieli, D. The control of the false discovery rate in multiple testing under dependency. Annals of Statistics 29, 1165–1188 (2001).

Bereznicki, S., Sobus, J., Vette, A., Stiegel, M., Williams, R. Assessing spatial and temporal variability of VOCs and PM-components in outdoor air during the Detroit Exposure and Aerosol Research Study (DEARS). Atmospheric Environment. 61: 159-168 (2012).

Brook, R., Bard, R., Burnett, R., Shin, H., Vette, A., Croghan, C., Stevens, C., Phillips, M., Williams, R. The associations between daily community and personal fine particulate matter levels with blood pressure and vascular function among non-smoking adults. Occupational and Environmental Medicine**.** 68:224-230 (2011a).

Brook, R.D, Rajagopalan, S., Pope, C.A. 3rd, Brook, J.R., Bhatnagar, A., Diez-Roux, A.V., Holguin, F., Hong, Y., Luepker, R.V., Mittleman, M.A., Peters, A., Siscovick, D., Smith, S.C. Jr, Whitsel, L., Kaufman, J.D. Particulate matter air pollution and cardiovascular disease: An update to the scientific statement from the American Heart Association. Circulation.1;121(21):2331-78 (2010).

Brook, R., Shin, H., Bard, R., Burnett, R., Vette, A., Croghan, C., Thornburg, J., Williams, R. Exploration of rapid effects of personal fine particulate matter exposure on hemodynamics and vascular function during the same day. Environmental Health Perspectives. 119: 688-694 (2011b).

752 Duval, R., Olson, D., Norris, G., Burke, J., Vedantham, R., Williams, R. Determining spatial
753 variability in PM2.5 source impacts across Detroit, MI. Atmospheric Environment 47: 491-498
754 (2012).
755
756 Edwards, R., Jurvelin, J., SAArela, K.,Jantunen, M. VOC concentrations measured in personal
757 samples and residential microenvironments in Expolis-Helsinki, Finland. Atmospheric
758 Environment 35, 4531-4543 (2001).
759
760 Fekedulegn, B. Desta; Colbert, J.J.; Hicks, R.R., Jr.; Schuckers, Michael E. Coping with
761 Multicollinearity: An Example on Application of Principal Components Regression in
762 Dendroecology. Newton Square, PA: U.S. Department of Agriculture, Forest Service,
763 Northeastern Research Station. p43 (2002).
764
765 George, B., Schultz, B., Palma, T., Vette, A., Williams, R. An evaluation of EPA's National-
766 Scale Air Toxics Assessment (NATA): Comparison with benzene measurements in Detroit,
767 Michigan. Atmospheric Environment 45: 3301-3308 (2011).
768
769 Hair, J.F. Jr., Black, W.C., Babin B.J., Anderson, R.E., Tatham, R.L.. Multivariate Data Analysis,
770 (Eds. 6). Pearson Prentice Hall, Upper Saddle River, New Jersey, US, pp. 115-122 (2005).
771
772 Hammond, D., Croghan, C., Shin, H., Burnett, R., Bard, R., Brook, R., Williams, R.
773 Cardiovascular impacts and micro-environmental exposure factors associated with continuous
774 personal PM2.5 monitoring. JESEE DOI:10.1038/jes.2013.46.(2013).
775
776 Hommel, G. A stagewise rejective multiple test procedure based on a modified Bonferroni test.
777 Biometrika 75, 383–386 (1988).
778
779 Kim, Y., Harrad, S., Harrison, R. Levels and sources of personal inhalation exposure to volatile
780 organic compounds. Environmental Science and Technology 36, 5405-5410 (2002)..
781
782 Lawless, P., Thornburg, J., Rodes, C., Vette, A., Williams, R. Personal exposure monitoring
783 wearing protocol compliance: an initial assessment of quantitative measurement. J. Exposure
784 Science and Environmental Epidemiology, 22: 274-280 (2012).

McClenny, W.A, Oliver, K.D., Jacumin, H.H. Jr., Daughtrey, E.H. Jr., Whitaker, D.A. 24 h diffusive sampling of toxic VOCs in air onto Carbopack X solid adsorbent followed by thermal desorption/GC/MS analysis – laboratory studies. J. Environ. Monit. 7, 248-256.(2005a).

McClenny, W.A, Oliver, K.D., Jacumin, H.H. Jr., Daughtrey, E.H. Jr., Whitaker, D.A. Comparison of 24 h averaged VOC monitoring results for residential indoor and outdoor air using Carbopack X-filled diffusive samplers and active sampling – a pilot study. J. Environ. Monit. 8: 263-269 (2005b).

Mohamed M. Shoukri, Mohammad A. Chaudhary. Analysis of Correlated Data with SAS and R (3rd edition), Chapman & Hall/CRC (2007).

Phillips, M., Rodes, C., Thornburg, J., Shamo, F., Whitmore, R., Chowdhury, D., Allpress, J., Vette, A., Williams, R. Optimizing recruitment and retention strategies for the Detroit Exposure and Aerosol Research Study (DEARS). RTI press.doi:10.3768/rtipress.2010.2010.mr0021.1011 (2010).

Rodes, C., Lawless, P., Thornburg, J., Croghan, C., Vette, A., Williams, R. DEARS particulate matter relationships for personal, indoor, outdoor, and central site settings for a general population cohort. Atmospheric Environment 44:1386-1399 (2010).

Stocco, C., MacNeill, M., Wang, D., Xu, X., Guay, M., Brook, J., Wheeler, A.J. Predicting personal exposure of Windsor, Ontario residents to volatile organic compounds using indoor measurements and survey data. Atmos. Environ. 42: 5905-5912 (2008).

Sexton K, Adgate JL, Church TR, Hecht SS, Ramachandran G, Greaves IA, et al. Children's exposure to environmental tobacco smoke: using diverse exposure metrics to document ethnic/racial differences. Environ Health Perspect;112:392–397 (2004a)..

Sexton K, Adgate JL, Ramachandran G, Pratt GC, Mongin SJ, Stock TH, et al. Comparison of personal, indoor, and outdoor exposures to hazardous air pollutants in three urban communities. Environ Sci Technol;38:423–430 (2004b).

818 Stevens, C., Williams, R., Jones, P. Progress on Understanding Spatial and Temporal
819 Variability of PM2.5 and its Components in the Detroit Exposure and Aerosol Research Study
820 (DEARS). Environ. Sci.: Processes Impacts, 16:94-105 (2014).
821
822 Snyder, R. Ethyl Browning's Toxicity and Metabolism of Industrial Solvents. (Eds 2). Volume 1:
823 Hydrocarbons. Amsterdam - New York - Oxford: Elsevier, p381(1987).
824
825 Wallace, L., Pellizzari, E., Hartwell, T., Sparacino, C., Zelon, H. Personal exposures, indoor-
826 outdoor relationships, and breath levels of toxic air pollutants measured for 335 persons in New
827 Jersey. Atmospheric Environment, 19, 1651-1661. (1985).
828
829 Weisel, CP, Zhang, J, Turpin, BJ, Morandi, MT, Colome, S, Stock, TH, Spektor, DM,et al.
830 Relationships of Indoor, Outdoor, and Personal Air (RIOPA): Part I. Collection Methods and
831 Descriptive Analyses. HEI Research Report 130; NUATRC Research Report 7. Heath Effects
832 Institute, Boston MA; Mickey Leland National Urban Air Toxics Research Center, Houston TX
833 (2005).
834
835 West B.T., Welch K.B., Galecki A.T. Linear Mixed Models, Chapman & Hall/CRC (2007).
836
837 Williams, R., Rea, A., Vette, A., Croghan C., Whitaker, D., Wilson, H., Stevens, C., McDow, S.,
838 Burke, J., Fortmann, R., Sheldon, L., Thornburg, J., Phillips, M., Lawless, P., Rodes, C.,
839 Daughtrey, H. The design and field implementation of the Detroit Exposure and Aerosol
840 Research Study (DEARS). Journal of Exposure Science and Environmental Epidemiology, 19:
841 643-659 (2009).
842
843 Williams, R., Jones, P., Carry Croghan, Thornburg, J., Rodes, C. The influence of human and
844 environmental exposure factors upon personal NO_2 exposure. J. Exposure Science and
845 Environmental Epidemiology 22: 109-115 (2012a).
846
847 Williams, R., Brook, RD., Bard, R., Hwashin, S., Burnett, R. Impact of nitrogen dioxide and
848 select particulate matter component concentrations on cardiovascular function alterations in a
849 general population. International J. Environmental Health Research, 22: No 1, 71-91 (2012b).
850

851

852

853

854

855