APPENDIX AVAILABLE ON THE HEI WEB SITE

Research Report 178

National Particle Component Toxicity (NPACT) Initiative Report on Cardiovascular Effects

Sverre Vedal et al.

Section 1: NPACT Epidemiologic Study of Components of Fine Particulate Matter and Cardiovascular Disease in the MESA and WHI-OS Cohorts

Appendix G. Data Analysis Plan for CIMT Longitudinal Analysis

Note: Appendices that are available only on the Web have been assigned letter identifiers that differ from the lettering in the original Investigators' Report. HEI has not changed the content of these documents, only their identifiers.

Appendix G was originally Appendix F

Correspondence may be addressed to Dr. Sverre Vedal, University of Washington, Department of Environmental and Occupational Health Sciences, Box 354695, 4225 Roosevelt Way NE, Suite 100, Seattle, WA 98105-6099; email: *svedal@uw.edu*.

Although this document was produced with partial funding by the United States Environmental Protection Agency under Assistance Award CR–83234701 to the Health Effects Institute, it has not been subjected to the Agency's peer and administrative review and therefore may not necessarily reflect the views of the Agency, and no official endorsement by it should be inferred. For the research funded under the National Particle Component Toxicity initiative, HEI received additional funds from the American Forest & Paper Association, American Iron and Steel Institute, American Petroleum Institute, ExxonMobil, and Public Service Electric and Gas. The contents of this document also have not been reviewed by private party institutions, including those that support the Health Effects Institute; therefore, it may not reflect the views or policies of these parties, and no endorsement by them should be inferred.

This document was reviewed by the HEI NPACT Review Panel but did not undergo the HEI scientific editing and production process.

APPENDIX F: Data Analysis Plan for CIMT longitudinal analysis

Title: Integrated epidemiologic and toxicologic cardiovascular studies to identify toxic components and sources of fine particulate matter

Brief Background: Many epidemiological studies reported the effect of traffic-related air pollution such as particulate matter (PM) on cardiovascular diseases. Further studies are needed to give more investigation on the association by using more specific measurements and richer dataset. This analysis aims to investigate how chemical components of PM2.5 in traffic exhaust emission would affect progression of atherosclerosis.

Objectives

1) Broad Objectives: To investigate long-term effect of PM2.5 chemical components in primary motor vehicle exhaust emissions on atherosclerosis in cross-sectional and longitudinal analyses

2) Specific Objectives (specific aims)

- To estimate effect of annual and cumulative predicted individual exposure to four PM2.5 components (elemental carbon (EC) and organic carbon (OC), sulfur (S), and silicon (Si) as markers of traffic-related combustion, secondary aerosol, and dust, respectively) on carotid intima-media thickness (CIMT)

- To compare effects of annual and cumulative predicted individual exposure of traffic related PM2.5 components (EC and OC) on CIMT with those of less traffic-related components (S and Si)

Statistical model

$$Y_{kit} = A_{ki} + \sum_{t'=1}^{t} B_{kit}(v_{kit'} - v_{ki(t'-1)}) + C_{kit} + \varepsilon_{kit}$$

$$A_{ki} = \alpha_0 + \alpha_1 X_{ki0} + \alpha_2 Z_{ki0} + a_{ki}$$

$$B_{kit} = \beta_0 + \beta_1 X_{ki0} + \beta_2 W_{kit'} + b_{ki}$$

$$C_{kit} = \gamma_2 U_{kit}$$

Outcome	Y_{kit}	: CIMT measurement for i-th person in k-th area at t-th follow-up visit
Cross-sectional (A_{ki})	X_{ki0}	: predicted PM2.5 component annual average at baseline
	Z_{ki0}	: covariates at baseline
	α_1	: cross-sectional effect of PM2.5 component on CIMT
Longitudinal (B_{kit})	v_{kit}	: time of t-th follow-up visit
	W_{kit}	: covariates between visits t and t-1
	β_1	: longitudinal effect of PM2.5 component on CIMT
Transitional (C_{kit})	U_{kit}	: time-varying covariates for adjustment of transient effects
	γ_2	: transient effect of time-varying covariates

- PM2.5 component concentration for the longitudinal part (B_{kit}) is identical to that used for the cross-sectional part (A_{ki}) as annual average at baseline (X_{ki0}) between Apr 2007 and Mar 2008 given limited monitoring data for one year and four months

Testable Hypotheses

- Effect of traffic-related component
  - Cross-sectional effect (α_1): Annual exposure to EC and OC is associated with increases in CIMT of subjects at baseline
  - Longitudinal effect (β_1): Cumulative exposure to EC and OCincreases CIMT
- Comparison between effects of traffic- and less traffic-related components
  - Cross-sectional effect (α_1): Annual exposure to S and Si does not increase or increases baseline CIMT less than EC and OC
  - Longitudinal effect (β_1): Cumulative exposure to S and Si does not increase CIMT or increases baseline CIMT less than EC and OC

Data

Outcome

- Far wall mean of the right common carotid at diastolic at MESA exam 1 to 3 (Jul.2000-Sep.2005)
- Only one follow-up exist at either exam 2 or 3
- We use re-read values for baseline (in the progression dataset), not initially-read (in the exam 1 main dataset)
- We do not use the IMT progression subset dataset (141 people), because they have different baseline values to those in the IMT progression main dataset

Exposure

- PM2.5 components: EC, OC, S, and Si
- Annual averages at each home address obtained from the spatio-temporal model constructed based on MESA Air monitoring data (no EPA data) between Apr 2007 and Mar 2008
- Annual average for each person calculated as weighted average across all home addresses over recorded residing period

Confounders (and precision variables)

- All variables considered for longitudinal analysis of PM2.5 and IMT (Adar et al 2011) as candidate covariates

- Primary variables will determined by variable selection which examines which covariates are associated with both the exposure metric and the outcome in areas of low exposure (see Variable selection section)

Population

- MESA Air participants living within 10 km from any monitors

Data exclusion for statin users

- Models will be run for PM2.5 on the full and exclusion (non-statin users) dataset using the same covariates, which will be selected on all people.
  - If the PM2.5 effect estimates differs by less than 20%, we will present analyses on the full cohort in our main models for PM2.5 component exposures with the excluded dataset as sensitivity analyses
  - If the PM2.5 effect estimate differs by more than 20%, we a priori decide to present the results for the restricted dataset of non-statin users, with the full dataset results as sensitivity

Analysis

1) Descriptive Analyses

- Summary of exposures
  - Summary statistics of within and between-city variability of monitoring exposure
  - Summary statistics of within and between-city predicted exposure
  - Summary statistics of CIMT, and covariates at baseline and follow-ups

2) Inferential Analyses

- Primary analyses
  1) Model 1 (minimally): PM2.5 components (alone), age, gender, and race
  2) Model 2 (moderately adjusted): model 1 + variables that are determined in variable selection and could not be affected by exposure (demographics, SES, anthropometry, and behavior on the table below)

3) Model 3 (main): Model 2 + variables that are determined in variable selection and could be affected by exposure

4) Model 4 (site) : Model 3 + site

- Sensitivity analyses

1) Fully specified model with additional variables

2) Model 3 + NO2/SO2

3) Statin users or full dataset results depending on the ‘Data exclusion for statin users’ section

4) Subjects residing within 5 km and 2 km from any MESA Air monitors as well as all without restriction

- Variable selection

1) A dataset of the "unexposed" will be defined based on being less than the median PM2.5 concentration at baseline and the median follow-up PM.25 concentration
2) Covariates will first be screened in univariate, cross-sectional analyses with IMT among the "unexposed". Variables with p-values < 0.2 will be included as potential confounders
3) Covariates that have met the definition as potential confounders cross-sectionally will be evaluated in longitudinal models among the "unexposed". Again a 0.2 significance level will be used, this time for b2.
4) Covariates selected under 2 and 3 will be evaluated for their association with PM2.5 using a simple regression model and a 0.2 significance cut-off.
5) Those variables that meet 2 and 4 (cross-sectional covariates) or 2,3, and 4 (longitudinal covariates) will be included in our models

Appendix Table F.1. The list of candidate covariates

Characteristics	Variables	Unit	Type of data	Data source	Time-Consistent vs. time-Varying
Demographic	Age+		Continuous	M.e1-3	C
	Race+		Categorical	M.e1-3	C
	Hispanic or not		Cat	C**	C
	Gender+		Cat	M.e1-3	C
	# people supported by family income		Con	M.e1-3	V
	Site+				V
Socioeconomic	Education		Cat	M.e1	C
	Income		Cat	M.e1-3	V
Anthropometry	Weight	lbs	Con	M.e1-3	V
	Height	cm	Con	M.e1-3	V
	Waist circumference	cm	Con	M.e1-3	V
	Hip circumference	cm	Con	M.e1-3	V
	Body surface area		Con	M.e1-3	V
	Body mass index	kg/m2	Con/Cat*	M.e1-3	V
Behavior	Cigarette smoking status		Cat	M.e1-3	V
	Cigarettes: average # smoked per day		Con	M.e1-3	V
	Pack-years of cigarette smoking		Con	M.e1-3	V
	Second-hand smoke		Con/Cat	M.e1-3/C	V
	Alcohol: current use		Cat	M.e1-3	V
	Total intentional exercise met-min/wk		Con	M.e1-3	V
Medical history	Hypertension		Cat	M.e1-3	V
	Family history of heart attack		Cat	M.e1	C
	Diabetes		Cat	M.e1-3	V
	Periodontitis or gum disease		Cat	M.e1	C
	Hypertension medication		Cat	M.e1-3	V
	Any lipid-lowering medication		Cat	M.e1-3	V
	Statin lipid-lowering medication		Cat	M.e1, Med.e2-3	V
BP/lipids/blood	SBP	mmhg	Con	M.e1-3	V
	DBP	mmhg	Con	M.e1-3	V
	HDL cholesterol	mg/dl	Con/Cat	M.e1-3	V
	LDL cholesterol	mg/dl	Con/Cat	M.e1-3	V
	Triglycerides	mg/dl	Con/Cat	M.e1-3	V
	Creatinine	mg/dl	Con	M.e1,3	V

	C-reactive protein	mg/L	Con	M.e1	C
	Fibrinogen antigen	mg/dl	Con	M.e1	C
	Fasting glucose	mg/dl	Con	M.e1-3	V
	Total homocysteine	nmo/IL	Con	M.e1	C
Neighborhood	Heavy traffic or speeding cars		Cat	M.e1	C
	Excessive noise		Cat	M.e1	C
	Years living in neighborhood		Con	M.e1	C
Diet	Vitamin		Con	D.e1	C
	Vitamin E		Con	D.e1	C
	Cod liver oil		Con	D.e1	C
Sex hormone	Sex hormone binding globulin	nmo/IL	Con	H.e1	C
	Bioavailable testosterone	nmo/IL	Con	H.e1	C

+ not included in the variable selection
* Con/Cat: there are both continuous and categorical variables
** Created variables