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Occup. Environ. Med. published online 21 Nov 2007;
doi:10.1136/oem.2007.035238

OEM Online First, published on November 21, 2007 as 10.1136/oem.2007.035238

Airborne particulate matter exposure and urinary albumin excretion:

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Key words: cardiovascular disease, environmental air pollutants, epidemiology
Word count: 4,083

Abstract

Objectives: Understanding mechanistic pathways linking airborne particle exposure to cardiovascular health is important for causal inference and setting environmental standards. We evaluated whether urinary albumin excretion, a subclinical marker of microvascular function which predicts cardiovascular events, was associated with ambient particle exposure.
Methods: Urinary albumin and creatinine were measured among members of the Multi-Ethnic Study of Atherosclerosis at three visits during 2000-2004. Exposure to $PM_{2.5}$ and PM_{10} ($\mu g/m^3$) was estimated from ambient monitors for one month, two months and two decades before visit one. We regressed recent and chronic (20 year) PM exposure on urinary albumin/creatinine ratio (UACR) (mg/g) and microalbuminuria at first exam, controlling for age; race/ethnicity; sex; smoking; secondhand smoke exposure; body mass index; and dietary protein (n=3,901). We also evaluated UACR changes and development of microalbuminuria between the first, and second and third visits which took place at 1.5 to 2 year intervals in relation to chronic PM exposure prior to baseline using mixed models.
Results: Chronic and recent particle exposures were not associated with current UACR nor microalbuminuria {per 10 $\mu g/m^3$ increment of chronic PM_{10} exposure, mean difference in log UACR = -0.02 (CI: -0.07, 0.03) and relative probability of having microalbuminuria = 0.92 (CI: 0.77, 1.08)} We found only weak evidence that albuminuria was accelerated among those chronically exposed to particles: each 10 $\mu g/m^3$ increment in chronic PM_{10} exposure was associated with a 1.14 relative probability of developing microalbuminuria over 3-4 years, though 95% confidence intervals (CI) included the null (0.96, 1.36).
Conclusions: UACR is not a strong mechanistic marker for air pollution's possible influence on cardiovascular health in this sample.

Abbreviations

AUC	area under the curve
BMI	body mass index
CI	confidence interval
EPA	Environmental Protection Agency
ETS	environmental tobacco smoke
km	kilometers
$\mu g/m^3$	micrograms per cubic meter
MESA	Multi-Ethnic Study of Atherosclerosis
PM	particulate matter
PM_{10}	particulate matter less than ten microns in aerodynamic diameter
$PM_{2.5}$	particulate matter less than 2.5 microns in aerodynamic diameter
UACR	urinary albumin/creatinine ratio

Main messages

- Cardiovascular-cause hospitalizations and deaths have been linked to exposure to particulate air pollution, and we explored urinary albumin levels as a novel potential marker for pollution exposure's contribution to development of cardiovascular disease.
- In this study, albumin excretion was not linked with either short or long-term exposure to particulate air pollution, and does not appear to be a strong mechanistic marker for air pollution's possible influence on cardiovascular health.

Policy implications

- Understanding biological mechanisms by which air pollution may contribute to cardiovascular morbidity and mortality is important for causal inference and helps form the evidence base for setting and enforcing protective air quality standards.
- Studying air pollution's effects on the cardiovascular health of a broadly representative multi-ethnic population is also important as many existing studies and cohorts do not reflect gender or race/ethnic diversity.
- Although our study did not show associations between air pollution exposure and albumin, ample evidence exists that pollution adversely affects the cardiovascular system, so other study designs or mechanistic pathways may be required to detect the signal of air pollution's contribution to deterioration of cardiovascular health.

Exposure to outdoor air pollution has been linked to a variety of adverse cardiovascular health outcomes. Long-term exposure to particulate matter (PM) measured at outdoor monitors has been associated with cardiovascular mortality.[1, 2] Shorter-term PM exposures have been linked with impaired vascular, autonomic and endothelial function [3-5] and enhanced inflammation, both pulmonary and systemic.[6, 7] Over time, repeated exposures to air pollution influencing these mechanisms may also lead to functional or structural changes in the cardiovascular system that may precipitate disease or even death.

Indicators of subclinical cardiovascular function allow investigation of the role of pollution exposure in early development of cardiovascular disease.[8] Urinary albumin excretion is one such indicator. Albumin is a medium sized protein typically filtered in the kidney by membranes and not found in the urine. However, when damage occurs in the glomerular endothelium and basement membrane, albumin is detectable in a urine sample.[9] Although cutoff points have been traditionally used to define unhealthy levels of urinary albumin (microalbuminuria), urinary albumin excretion predicts cardiovascular risk in the general population, across the full range of urinary levels, even those below clinically defined dysfunction.[10-12] Because leakage of albumin across membranes in the kidney can also reflect loss of arterial integrity in other vascular beds, albumin in urine can be a useful generalized marker of vascular function [12, 13] and a screening tool for risk of cardiovascular events.[10] Urinary albumin has been linked with impaired endothelial function, peripheral vascular disease and other related conditions.[10, 12]

Evidence that PM exposure is associated with development of albuminuria would suggest that changes in vascular function mediate associations between PM exposures and cardiovascular disease deaths or events. PM exposure affects systemic vascular health indicators correlated with urinary albumin, implying a plausible link. For example, environmental tobacco smoke (ETS), which has similar characteristics to ambient PM, has been associated with impaired endothelium-dependent dilation among healthy adults [14] and with vascular reactivity in rats.[15] Ambient PM pollution has been linked with reduced endothelial function in humans,[5] and direct smoking can be a risk factor for impaired kidney function.[16] This and other evidence implies that PM exposures may affect vascular health, via oxidative stress or other mechanisms.[17] Urinary albumin excretion levels can change over periods of weeks, months or years, reflecting changes in systemic microvascular health and overall endothelial function.[16, 18, 19] Studying urinary albumin excretion allows testing of whether changes in systemic vascular function mediate the effects of PM exposure on cardiovascular risk.

Using data from the Multi-Ethnic Study of Atherosclerosis (MESA), a large epidemiologic study of subclinical cardiovascular disease, we investigated whether ambient particle exposure is associated with urinary albumin excretion. The time lags with which PM exposure may affect vascular function (and albumin excretion) are unknown. Therefore we investigated both chronic (20 year) and recent (prior 30 and 60 day) exposures as predictors of albuminuria. We also examined heterogeneity of these associations by race-ethnicity, age, sex, and study site.

METHODS

Study population

MESA is an ongoing longitudinal study of subclinical atherosclerosis funded by the National Heart Lung and Blood Institute.[20] Cohort members are 6,814 men and women aged 44-84 who were free of clinical cardiovascular disease at baseline. Individuals were recruited from six field centers: Baltimore, MD (Johns Hopkins); Chicago, IL (Northwestern); Forsyth County, NC (Wake Forest); Los Angeles, CA (University of California-Los Angeles); New York, NY (Columbia); and St. Paul, MN (University of Minnesota). Additional details on study design are provided elsewhere.[20] These analyses are based on data collected at the baseline visit (June 2000-August 2002) and the second and third visits, which took place at 1.5 to 2 year intervals after baseline.

Creatinine-adjusted urinary albumin excretion

Our outcome of interest was creatinine-adjusted urinary albumin excretion. For MESA participants, urinary albumin and creatinine levels (mg/dl) were measured in a spot sample taken in a fasting state at the baseline exam. Samples were analyzed using nephelometry (albumin) and the rate Jaffe reaction (creatinine) at a central laboratory following standard quality assurance and control procedures and uniform storage and transport protocols.[21] The urinary albumin/creatinine ratio (UACR) was calculated and adjusted for sex-specific differences in creatinine excretion by dividing the ratio by 0.68 for men because of their typically larger size and muscle mass.[22] MESA participants were classified into four categories of urine albumin excretion (normal, high normal, microalbuminuria, and macroalbuminuria), following Murtaugh et al.[23]

Air pollution exposure

Both recent and chronic PM exposures were investigated. Recent exposure was assigned based on the participant's place of residence at the time of the baseline exam. Chronic exposure was estimated based on a residential history reported by each participant as part of an ancillary study to MESA. Participants reported all residential addresses since January 1982, including move dates (month and year). All addresses were geocoded, creating a file containing the residential location for each participant for each month between January 1982 and the date of the baseline exam.

Data on air pollution from community monitors sited for regulatory purposes were obtained from the EPA Aerometric Information Retrieval Service (AIRS) database. For recent exposures we investigated mean concentrations, in $\mu g/m^3$, of particles less than 10 and 2.5 microns in aerodynamic diameter, respectively ($PM_{10,}$ $PM_{2.5}$) for two time periods prior to the baseline exam: the average of the prior month, and average of the prior two months. Particle monitors collected 24-hour integrated samples, some daily but most every third day. Based on reported residence of MESA participants at the time of the baseline exam, average monthly exposures were assigned using the nearest monitor with available data on that day (i.e., for each day of the prior month or two months). The mean distance to the nearest monitor was 9 kilometers (range 0.45-51 kilometers).

Longer term exposure was estimated for PM_{10} and $PM_{2.5}$ in two ways. The EPA monitoring network has made direct measurements of PM_{10} over a longer time frame than $PM_{2.5,}$ so one metric of cumulative 20 year PM_{10} exposure was estimated with data from those direct monitor readings. The nearest monitor to each participant's residential address was used to compute monthly exposure averages from January 1982 to December 2002 (or the date of the baseline exam, if it came first). An area under the curve (AUC) calculation is used to represent an average concentration over a time interval; 20 years in our study. If we plot the monthly average estimated pollution concentration for each participant over the period of the study, and take the area under that curve, we have an estimate of his or her exposure in ug/m^3. This method is an advantage over a simple average of concentrations over the time period because it allows interpolation of exposure over months with missing data, although this was a very small number in our dataset. However, we chose to use this AUC method for comparability with our imputed PM exposures (described next). The specific calculation was done as follows: Starting with the first available date, each average monthly PM_{10} value was multiplied by the number of months the subject was exposed to this value. If PM_{10} information was missing (skips), the missing month(s) were given the average of the PM_{10} value from immediately before the skip and immediately after the skip. This average value was multiplied by the size of the skip. All values were summed and then divided by the overall number of exposure months to get a cumulative monthly average over the 20 years. The results were reported per 10 ug/m^3 increments in PM_{10}, as is standard in air pollution epidemiology..

In addition to long-term PM_{10} estimates based solely on direct monitor readings, cumulative $PM_{2.5}$ and PM_{10} exposures were imputed using a space-time model which yielded a three-dimensional exposure 'surface' of pollution concentrations over the continental U.S. for each month during the 20 year exposure period. Predictor variables for this estimated surface included: monitored PM levels and other covariates, including temperature and airport visibility data obtained from the National Climatic Data Center, total suspended particle measures from EPA's network, and population density from the 1990 U.S. Census.[24] This space-time model captured variation over time using trend, cyclic and autoregressive terms, and thin plate splines were used to capture variation over space. With the nation-wide exposure surface created from the space-time model, each MESA participant was assigned a multiply-imputed cumulative exposure based on the months and locations represented in the residential history data. Multiple imputation has the advantage over using a single imputation in that the standard errors correctly reflect the level of uncertainty inherent in estimating missing values[25]; we followed standard multiple imputation procedures for this model. The overall fit of the space-time model with the observed data (for PM_{10}) is characterized by an R-square of 58%. The model was also validated by deleting 10% of the observed values, imputing them and then comparing the distributions of imputed and observed values. A scatter plot of the imputed and observed values showed a scatter around a 45 degree line. The cumulative imputed 20 year exposures to $PM_{2.5}$ and PM_{10} were represented by an AUC, as for the directly-monitored PM_{10} estimate.

Other covariates

During the baseline MESA exam, participants provided detailed information on personal characteristics (sex, age, race/ethnicity; cigarette smoking (never, former, current); and dietary protein). Height and weight were measured using standard procedures and used to calculate body mass index (BMI). MESA participants also reported ETS exposure in the year prior to the

baseline exam (were they in 'close quarters' with a person who smoked, at home, at work, in a car, etc.), in hours per week.

Analytical approach

We evaluated associations of chronic and recent PM exposure with two outcomes measured at the MESA baseline visit: continuous log UACR and clinically defined micro- or macro-albuminuria [23] (UACR $\geq$ 25 mg/g) vs. normal levels. We used scatter-plots to examine associations of the exposure measures with the baseline log UACR and calculated descriptive statistics and correlations between air pollution variables, and bivariate associations between covariates and log-transformed UACR. We used multiple linear regressions to estimate associations of PM exposures with log UACR after adjustment for age, sex, race/ethnicity, BMI, percent dietary protein, cigarette smoking (never, former, current) , and ETS exposure (<1 hour/week, $\geq$1 hour/ week). Although systolic and diastolic blood pressure, use of blood pressure medication, inflammatory markers, and diabetes status were available as potential covariates, we did not adjust for them, as they have been associated with air pollution exposure in previous studies and are potentially along the mechanistic pathway linking air pollution exposure to UACR. We expressed results as mean differences in log UACR at the baseline exam associated with a 10 ug/m^3 increase in particle exposure. We used binomial regression [25] to evaluate whether air pollution was associated with microalbuminuria compared to normal and high-normal UACR levels, expressed as a relative probability per 10 ug/m^3 increase in PM exposure. Analyses using imputed datasets used appropriate methods to account for uncertainty in the imputations.[26]

To evaluate whether long-term PM exposure was associated with albumin changes over the three exam visits, we fit repeated measures model with random subject effects to estimate three-year changes in log UACR by levels of exposure. The repeat measures models included time in years, quartiles of long-term PM exposure (based on the directly estimated PM_{10} AUC measures), interactions between time and PM_{10} exposure category, and all the baseline covariates included in the cross-sectional analyses. We also examined sensitivity of results to the inclusion of time-by-baseline covariate interactions to allow the change over time to differ by covariate levels. The three-year change in log UACR among participants in each exposure quartile was represented by the slope associated with time plus the corresponding time by exposure interaction. We also estimated the relative probability that MESA participants who did not have microalbuminuria at baseline would develop the condition at exams 2 or 3, per 10 ug/m^3 increase in estimated long-term exposure to directly-monitored $PM_{10,}$ using log-binomial regression models fit with SAS PROC GENMOD.[26]

We examined heterogeneity of effects by sex; race/ethnicity; study site; and age in all models by including the corresponding interaction term(s) in fully adjusted models. Albumin excretion differs by sex,[9] and associations between particle pollution and carotid intima-media thickness (CIMT), another subclinical indicator of cardiovascular function, were stronger among women.[27] Associations between air pollution and heart rate variability have differed by race and ethnicity.[28] Study site was evaluated because pollutant mix and composition (including oxidative properties of PM [29] can differ greatly by location. Age may indicate differing susceptibility to the effects of air pollution on vascular function. We defined effect modification as present if the p value for the interaction term was less than 0.01.

In sensitivity analyses, we examined these associations among individuals whose exposure to directly monitored $PM_{2.5}$ and PM_{10} was estimated from monitors located within 10 kilometers of their residences, for all exposure timeframes. For two decade exposures we also contrasted results using observed PM data to those obtained with multiply-imputed exposures from the space-time model.

Of the 6814 participants recruited to MESA, 5,229 had complete data on the outcome and clinical covariates used for the analyses and had completed the residential history questionnaire. Of these, 4,343 had geocodes available for all residential addresses between August 1982 and August 2002 and thus complete data on the chronic exposures. For comparability between the estimates for the long-term exposure and estimates for short-term exposure, analyses were further restricted to individuals for whom exposure could be assigned on all timescales. This yielded a total of 3,901 participants for analysis.

RESULTS

Demographic and clinical characteristics of the sample are provided in Table 1. Just over half the study sample were women, and the average age of participants was 63. Fifty percent of the participants had ever smoked, and about 36% reported any ETS exposure. On average, dietary protein made up approximately 16% of daily energy intake, and the mean BMI of the analysis population was 28.4. The majority of the participants (78.7%) had UACR considered normal, and around 20% were classified as having microalbuminuria or high-normal levels, with just 1% at the macroalbuminuria level. There were no important differences in key characteristics when the analysis sample was compared with the full MESA cohort (n = 6,814). The study sample had a lower representation from St. Paul compared to the full sample (8.0% vs. 15.6%), and less Chinese and Hispanic participants than the full cohort (11.8% vs. 21.9%), because many of these people were recent immigrants whose chronic exposure could not be estimated.

Table 1 Demographic and clinical characteristics and urinary albumin/creatinine ratio for participants included in the analyses (n=3,901); MESA 2000-2002

Age, years (mean±SD)		63.04 ± 9.9
% Female		52.4%
Race/ethnicity (% distribution)	Caucasian	41.2%
	Chinese	8.5%
	African American	30.5%
	Hispanic	19.8%
Study site (% distribution)	Baltimore	17.8%
	Chicago	21.0%
	Forsyth County	18.8%
	Los Angeles	18.5%
	New York City	15.9%
	St. Paul	8.0%
Body mass index, kg/m^2 (mean±SD)		28.4 ± 5.3
Dietary protein (mean ±SD)	Percent of total calories	16.0 ± 3.7
Smoking status (% distribution)	Never	50.2%
	Former	38.4%
	Current	11.4%
Environmental tobacco smoke (ETS) exposure	None	64.1%
	At least one hour per week	35.9%
Urinary albumin/creatinine ratio (UACR) mg/g [a] (median±SD)	Visit 1	4.6 ± 99.1
	Visit 2	4.8 ± 97.5
	Visit 3	5.4 ± 100.3
UACR categories (mg/g) (based on visit 1 levels)		
Normal (< 15)		78.7%
High normal (≥15, <25)		10.3%
Microalbuminuria (≥25, <250)		10.0%
Macroalbuminuria (≥ 250)		1.0%

[a] Exam1 N=3901, Exam2 N=3899, Exam3 N=3708

Pollution levels measured the two decades and month prior to the MESA baseline exam are reported in Table 2. The five-year increments that comprise the twenty-year cumulative PM_{10} assigned to participants reflect overall decreasing trends in PM_{10} levels across the U.S. during these decades.

Table 2. Pollutant exposures for study participants by enrollment site for previous month and previous 20 years (based on residential history)

Pollutant[a]	Exposure period	Location	N	mean	s.d. [b]
PM_{10}	1982-2002	All sites	3901	34.7	7.0
	1982-1987	All sites	3901	40.5	7.5
	1988-1992	All sites	3901	38.0	8.9
	1993-1997	All sites	3901	30.6	7.3
	1998-2002	All sites	3901	29.7	6.9
	Previous month	All sites	3901	27.5	7.9
		Baltimore	695	22.7	6.4
		Chicago	818	31.7	7.9
		Forsyth	733	22.4	5.2
		Los Angeles	721	33.1	7.0
		New York	621	25.2	6.1
		St. Paul	313	31.3	4.0
$PM_{2.5}$	Previous month	All sites	3901	16.5	4.8
		Baltimore	695	15.9	3.6
		Chicago	818	16.7	3.9
		Forsyth	733	15.2	3.4
		Los Angeles	721	21.8	5.3
		New York	621	15.5	2.8
		St. Paul	313	10.4	2.5

[a] in units of $\mu g/m^3$

[b] standard deviation

In a linear regression model not including the pollutant values, UACR was significantly higher among: older participants; men; those of Chinese and Hispanic ethnicity compared to Caucasians; those with higher dietary protein intake, and those with higher BMI. Current smokers had an adjusted mean difference in UACR of 0.145 (95% CI: 0.033, 0.257) compared to never smokers. For former smokers compared to never smokers, the adjusted mean difference was 0.025 (95% CI: -0.048, 0.098). The point estimate of the association of UACR with ETS was positive though the confidence intervals included the null value. Scatter-plots of the albumin variables and pollution exposures revealed no apparent patterns of associations (not shown).

Adjusted mean differences in log UACR associated with the pollutant exposures studied are shown in Table 3, for the total sample and the 2,611 participants living within 10 kilometers of a monitor for all exposure metrics. The estimated associations are mostly negative, and for all but one of the models examined (60 day prior PM_{10} exposures), confidence intervals included the null. Except for the association with imputed cumulative $PM_{2.5}$ exposure, restricting to the population living in closer proximity to monitors pulled the point estimates of effect consistently closer to 0 or upward.

Table 3. Adjusted[a] mean differences in log urinary albumin/creatinine ratio (UACR), (mg/g), per 10 μg/m^3 increase in particulate matter among MESA participants seen at baseline visit from 2000-2002.

Pollutant and exposure period	Population[b]	Mean difference	95% Confidence interval	
$PM_{2.5}$				
Prior 30 days	full sample	-0.017	-0.087	0.052
	within 10 km	0.026	-0.067	0.119
Prior 60 days	full sample	-0.040	-0.121	0.042
	within 10 km	-0.013	-0.122	0.097
PM_{10}				
Prior 30 days	full sample	-0.042	-0.085	0.002
	within 10 km	-0.023	-0.079	0.034
Prior 60 days	full sample	-0.056	-0.106	-0.005
	within 10 km	-0.040	-0.106	0.025
Prior 2 decade exposure (1982-2002), from area under the curve for monthly levels				
PM_{10} from nearest monitors	full sample	-0.019	-0.072	0.033
	within 10 km	0.009	-0.067	0.085
Imputed exposures[c]				
PM_{10}	full sample	-0.002	-0.038	0.035
	within 10 km	0.016	-0.033	0.066
$PM_{2.5}$	full sample	0.002	-0.048	0.052
	within 10 km	-0.012	-0.076	0.053

[a] Adjustment: Baseline covariates (degrees of freedom): Age (1), gender (1), race (3), BMI (1), cigarette status never-former-current (2), environmental tobacco smoke exposure (1), percent dietary protein (1).

[b] Population: Full sample (n=3,901) had exposure estimated using nearest monitor, regardless of distance from reported residential address. 2,611 participants lived within 10 km of monitors

[c] Imputations from time-space model using monitor data, temperature and visibility (see text) These imputations did not use the nearest monitor approach but are reported for the two populations, defined by monitor proximity, for comparison with the other estimates.

The adjusted relative probability of having microalbuminuria at baseline according to recent and chronic PM exposures are shown in Table 4. As for the continuous UACR, the majority of the point estimates of effect were in the opposite of the hypothesized direction, and all but one of the estimates (for PM_{10} exposure in the prior 60 days) had a confidence interval including the null.

Table 4. Adjusted[a] relative prevalence of microalbuminuria[b] vs. high-normal and normal levels (below 25 mg/g), per 10 μg/m^3 increment in particulate matter, among 3,864 MESA participants without macroalbuminuria seen at baseline visit, 2000-2002.

Pollutant and exposure period	Relative prevalence	95% CI[c]	
$PM_{2.5}$			
Prior 30 days	0.94	0.77	1.16
Prior 60 days	0.90	0.71	1.14
PM_{10}			
Prior 30 days	0.88	0.76	1.02
Prior 60 days	0.83	0.70	0.99
Prior 2 decade exposure (1982-2002), from area under the curve for monthly levels			
PM_{10} from nearest monitors	0.92	0.77	1.08
Imputed exposuresd			
PM_{10}	0.98	0.87	1.10
$PM_{2.5}$	0.98	0.84	1.14

[a] Adjustment : Baseline covariates (degrees of freedom): Age (1), gender (1), race (3), BMI (1), cigarette status (never-former-current) (2), environmental tobacco smoke exposure (1), percent dietary protein (1)

[b] Albuminuria defined as UACR $\geq$ 25 mg/g; macro-albuminuria $\geq$ 250 mg/g

[c] Confidence interval

[d] Imputations from time-space model (see text)

Similarly, when analyzing albumin levels at all three exams, the adjusted relative probability of developing microalbuminuria over the follow-up period associated with a 10 μg/m^3 difference in chronic PM_{10} exposure was elevated (1.14, 95% CI: 0.96, 1.36) but confidence intervals included the null, even when the population was restricted by monitor proximity (1.06, 95% CI: 0.84, 1.35). Results using discrete survival analysis, with and without accounting for unequal exam intervals, were virtually identical to those reported above using binomial regression (not shown).

The repeated-measures analysis of change in continuous log UACR by quartile of long-term exposure showed a positive slope among all exposure quartiles (Table 5). Restricting the models to participants living closer to ambient monitors did not have a consistent influence on the estimated slopes. The slopes increased monotonically by increasing exposure quartile for the full-sample analyses, but the p-value for trend in that set of analyses was 0.42, and p-values for trend were similarly non-significant in the other model. Inclusion of interaction terms between time and other covariates had little influence on the pattern or significance of the estimates.

Table 5. Adjusted[a] mean 3 year change in log UACR (mg/g) by quartiles of 1982-2002 exposure to PM_{10} from ambient monitors among MESA participants seen from 2000-2004.

Population[b]	Quartile of PM_{10} in $\mu g/m^3$ from area under the curve	Slope	Standard error	Test for Trend (p-value)
full sample	Range (18.5, <29.3)	0.147	0.024	0.42
	Range (29.3, <33.1)	0.159	0.024	
	Range (33.1, <36.3)	0.163	0.024	
	Range (36.3, 55.7)	0.174	0.023	
within 10 km	Range (18.5, <29.3)	0.159	0.030	0.99
	Range (29.3, <33.1)	0.155	0.031	
	Range (33.1, <36.3)	0.167	0.028	
	Range (36.3, 55.7)	0.152	0.036	

[a] Adjustment variables: Baseline covariates (degrees of freedom): Age (1), gender (1), race (3), BMI (1), cigarette status never-former-current (2), environmental tobacco smoke exposure (1), percent dietary protein (1), and interaction terms between time (years) and PM_{10} exposure

[b] Population: The full sample (n = 3,901) had exposure estimated using nearest monitor, regardless of distance from reported residential address. 2,611 participants lived within 10 km of monitors; 2,497 had exam 3 data.

Heterogeneity by gender, age, race/ethnicity, and site was examined in fully adjusted models for both shorter-term exposures and 20 year PM_{10} exposure. Interactions with PM exposure were not significant (by the $p < .01$ criterion) by gender, age, race/ethnicity, or study site.

DISCUSSION

Chronic and recent exposures to ambient particles were not associated with urinary albumin excretion in our sample. There was only weak evidence that long-term exposure is associated with changes in microalbuminuria over time. This study is the first that we know of to examine albumin excretion as a subclinical indicator of the potential impact of air pollution on vascular function in a multi-ethnic population. Our results suggest that urinary albumin is not a marker for a primary mechanism underlying the population-level observations of increased cardiovascular morbidity and mortality associated with air pollution exposure. Associations showed little evidence for effect modification by sex, race/ethnicity, study site and age.

Although several studies have examined short-term pollution exposure and biomarkers of cardiovascular function, few studies of subclinical disease indicators and chronic pollution exposure exist. Higher CIMT, a structural marker of subclinical cardiovascular disease, was seen among those living in areas of Los Angeles with higher estimated outdoor fine particle levels.[27] Urinary albumin provides information about both functional and structural aspects of cardiovascular health, specifically marking smaller arteries, and complements this research.[30, 31]

Urinary albumin excretion has traditionally been used as a screening tool to determine progression of deteriorating vascular function. Higher levels of albumin in urine result from physiologic changes including increased blood pressure in the glomerulus; and charge changes in the glomerular capillary basement membrane, possibly due to glycosylation of proteins in the membrane.[16] Albumin levels are well-correlated with microvascular dysfunction.[19]

Within-individual fluctuations in levels of albumin excretion occur (even including reductions in albumin excretion termed 'regression' from microalbuminuria to normoalbuminuria [18]. Predictors of acute changes in albumin excretion include protein intake, blood pressure, CRP, and insulin resistance [32-34] and changes have typically been evaluated at intervals of weeks to months. Because of limited knowledge of the timescale of changes in urinary albumin excretion, we evaluated air pollution exposure at various timescales ranging from the potential effects of long-term cumulative exposures over 20 years, to more recent exposures in the prior two months.

Albumin excretion measures have limitations. We had only a single spot urine sample for this study, and important variations may not be well captured by this technique, even with adjustment for creatinine.[21] Urinary albumin excretion can be measured using a timed collection interval (considered the 'gold standard') or a single sample collected in a morning visit and adjusted for urinary creatinine, a metabolic byproduct of muscle.[35] Adjusting the albumin concentration for creatinine levels is common practice for a spot sample, since creatinine concentration is fairly constant throughout the day and a good indicator of urine flow rate.[36] Although some variation by race exists in creatinine excretion, these differences have been evaluated only for Blacks and Whites, not Asians or Hispanics, so no race-specific adjustment was done, consistent with a previous analysis in the MESA cohort.[21] In spite of limitations of spot samples,[37] many previous studies show their predictive power for cardiovascular events, and the UACR values in this population were associated with known risk factors for microalbuminuria in the expected direction.

Measurement error in assigning environmental exposure to participants may have hampered our ability to detect associations with albumin, especially if any true causal effects are small. The ideal exposure metric would be a direct measure of personal air pollution exposure of MESA participants over the months and the two decades prior to the baseline exam. No study has yet measured personal pollution exposure for such a long period of time. While our PM measure is imperfect, previous studies have found associations between PM exposure and cardiovascular events and mortality using exposure measures cruder than ours (e.g., a single urban monitor, average of a few urban monitors), controlling for other known risk factors).[1, 2] Assigning exposures for or each month based on the nearest monitor is an improvement over a single-monitor approach. Although strong evidence exists that daily fluctuations in ambient PM may precipitate cardiovascular events, the effect of PM in the process of developing cardiovascular disease is likely be a weaker signal and thus difficult to detect.

This study did not account for exposures occurring during commuting or at the workplace. However, ambient (background) PM tends to be a spatially homogeneous pollutant, relative to gaseous pollutants, so background exposures are likely to be fairly well-represented by ambient monitor measures [38] and the majority of MESA participants report spending 60% of their time at home or within two kilometers of their home.[39] We found no differences in the results when analyses were restricted to persons within 10 kilometers of a monitor for the full exposure period, or using space-time models to impute cumulative exposure to both PM size fractions. Outdoor ambient measures of PM were more strongly associated with cardiopulmonary health outcomes than indoor or non-ambient personal exposures,[40] thus supporting the importance of our analysis using ambient PM measurements used to enforce community air pollution standards.

A new study linked to the MESA cohort will allow much more detailed assessment of exposure using time-activity diaries and additional fixed and person-level monitoring. These data

will allow assessment of the relationship between short-term changes in PM and short-term changes in albumin excretion as cohort follow-up continues. More complex exposure assignment schemes, including incorporating distance to roadways and traffic counts, may yield different results in future efforts to model chronic exposure in MESA, and facilitate detection of the signal of air pollution's impact on subclinical disease processes. However, similar exposure assignment techniques to the present study have been used in landmark studies showing robust associations between long-term pollution exposure and mortality.[1, 2]

Our longitudinal analyses examined the relationship between long-term cumulative exposure and subsequent changes in albumin excretion over a 3-4 year period. The objective was to determine whether long-term cumulative exposure places persons on a trajectory of deteriorating vascular function. These analyses examine the relationship between long-term exposure and within-person change. Although imprecise, the point estimates for development of microalbuminuria and slopes for change in continuously measured UACR were consistent with our hypothesis that vascular deterioration would be accelerated among those with higher chronic exposures to pollution.

CONCLUSIONS

We examined associations between air pollution and UACR in a large, multi-ethnic sample with a substantial age range and ethnic diversity, and information on a variety of covariates. Our objective was to explore a novel potential mechanistic pathway to aid in evaluating the causal links between pollution exposure and cardiovascular health seen in numerous epidemiologic studies. Although prior evidence from other studies suggests that particulate pollution exposure may contribute to progression of renal disease and vascular dysfunction over and above the standard risk factors, we did not see evidence for this in MESA. Our findings do not strongly support the use of UACR as a marker of microvascular function to understand the cardiovascular effects of air pollution exposure, but pollution exposure may be associated with increased albumin excretion in vulnerable subgroups, or in studies with more detailed measures of personal exposures.

ACKNOWLEDGMENTS, FUNDING AND COMPETING INTERESTS

The Multi-Ethnic Study of Atherosclerosis (MESA) is supported by contracts N01-HC-95159 through N01-HC-95165 and N01-HC-95169 from the National Heart Lung and Blood Institute. This work was supported by grant R830543 (Principal Investigator Ana V. Diez Roux) from the U.S. Environmental Protection Agency and the Robert Wood Johnson Health & Society Scholars Program. The authors thank the other investigators, the staff, and the participants of the MESA study for their valuable contributions, and Irina Mordukhovich for formatting assistance. A full list of participating MESA investigators and institutions can be found at http://www.mesa-nhlbi.org. The authors have no competing interests to declare.

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