

## Introduction

Terminal duct lobular units (TDLUs) naturally involute with age (number and size) and are the structures within the breast where most cancers arise

Reduced TDLU involution has been associated with an increased risk of breast cancer

Outdoor air pollution has been related to elevated breast cancer risk

Studying the relationship between air pollution and TDLU involution may inform mechanisms underlying the association between air pollution and breast cancer risk

No epidemiologic studies to date have examined this question

## Objective

Determine whether air pollution was associated with measures of TDLU involution (TDLU count, TDLU span, and acini/TDLU) in normal breast tissue samples

We considered PM<sub>2.5</sub> total mass, components of PM<sub>2.5</sub>, clusters of participants by PM<sub>2.5</sub> component profiles, and gaseous pollutants

## Study design

### Population

1,908 women ages 18 to 75 years who donated tissue to the Komen Tissue Bank in 2009-2012 and had measures of TDLU involution

### Exposure Assessment

Primary exposure: 2009 PM<sub>2.5</sub> concentrations determined at a 12x12 km grid level and linked to each woman's geocoded residential address

Estimated from EPA's Bayesian space-time Downscaler Model combining Community Multiscale Air Quality (CMAQ) modeling with fixed measurements from monitors

Secondary exposures (CMAQ modeling only): components of PM<sub>2.5</sub> (SO<sub>4</sub>, NO<sub>3</sub>, NH<sub>4</sub>, EC, OC) and gaseous pollutants (CO, NO, NO<sub>2</sub>, SO<sub>2</sub>)

### Outcome Assessment

Four breast tissue cores were collected from the upper outer quadrant of the breast with a standard 10-gauge needle; one core was fixed

A pathologist enumerated TDLUs; among women with >0 TDLUs, 10 TDLUs were measured for median TDLU span and acini/TDLU

## Statistical analysis

### Individual Pollutant Analysis

TDLU count: zero-inflated negative binomial regression models to estimate relative rates (RRs) and 95% confidence intervals (95% CIs)

TDLU span and acini/TDLU: ordinal logistic regression models to estimate odds ratios (ORs) and 95% CIs

Examined associations overall and by menopausal status

### PM<sub>2.5</sub> Component Clusters

K-means clustering to identify clusters of individuals with similar patterns of PM<sub>2.5</sub> component exposure

Compared concentrations of components, participant characteristics, and geographic variations in clusters. Examined associations with TDLU measures

### Confounders

Age, education, smoking status, race/ethnicity, body mass index, % of fat on the slide

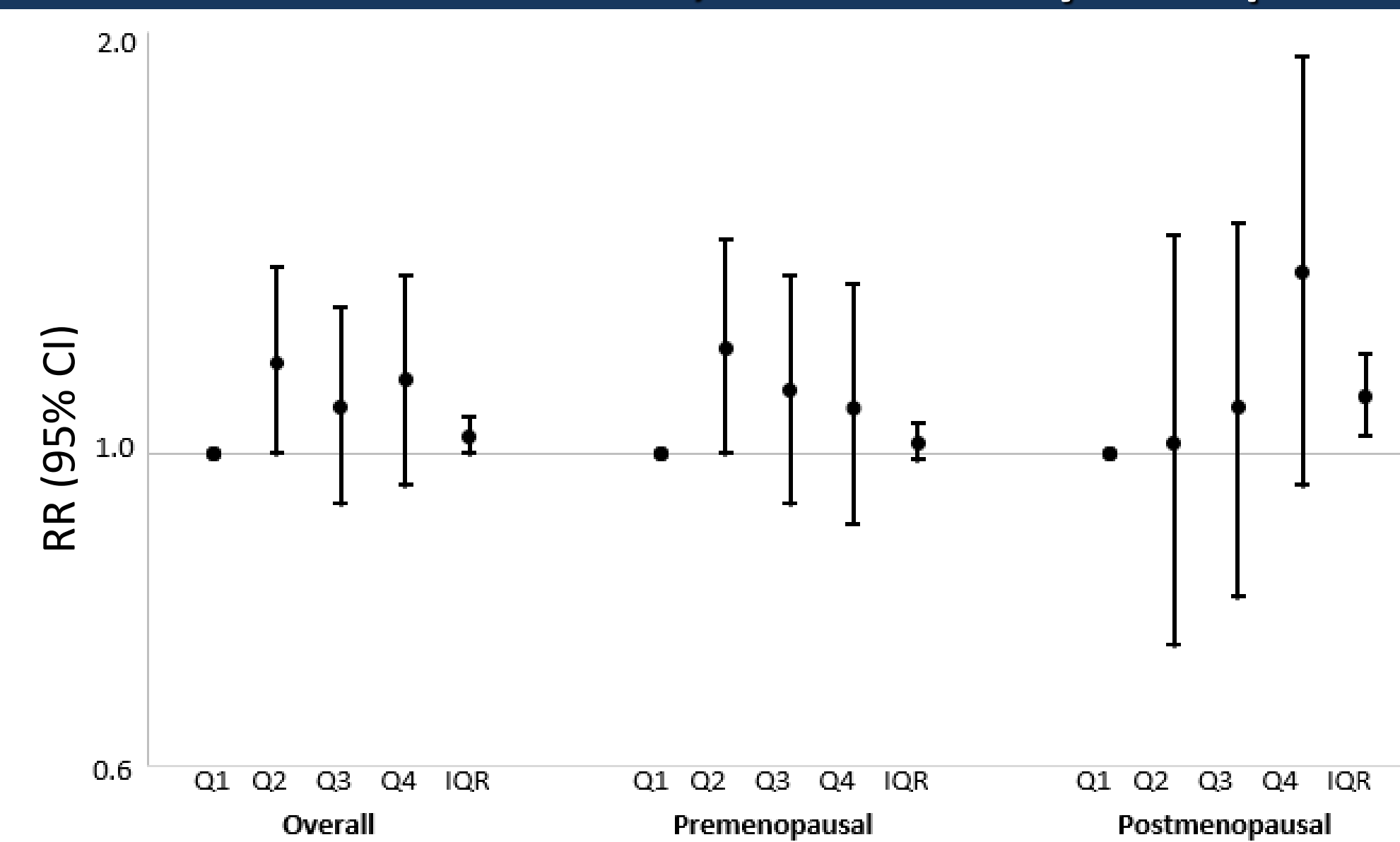
## PM<sub>2.5</sub> was associated with reduced TDLU involution of the breast

## Air pollution may influence histologic characteristics of normal breast tissue and thus increase susceptibility to breast cancer

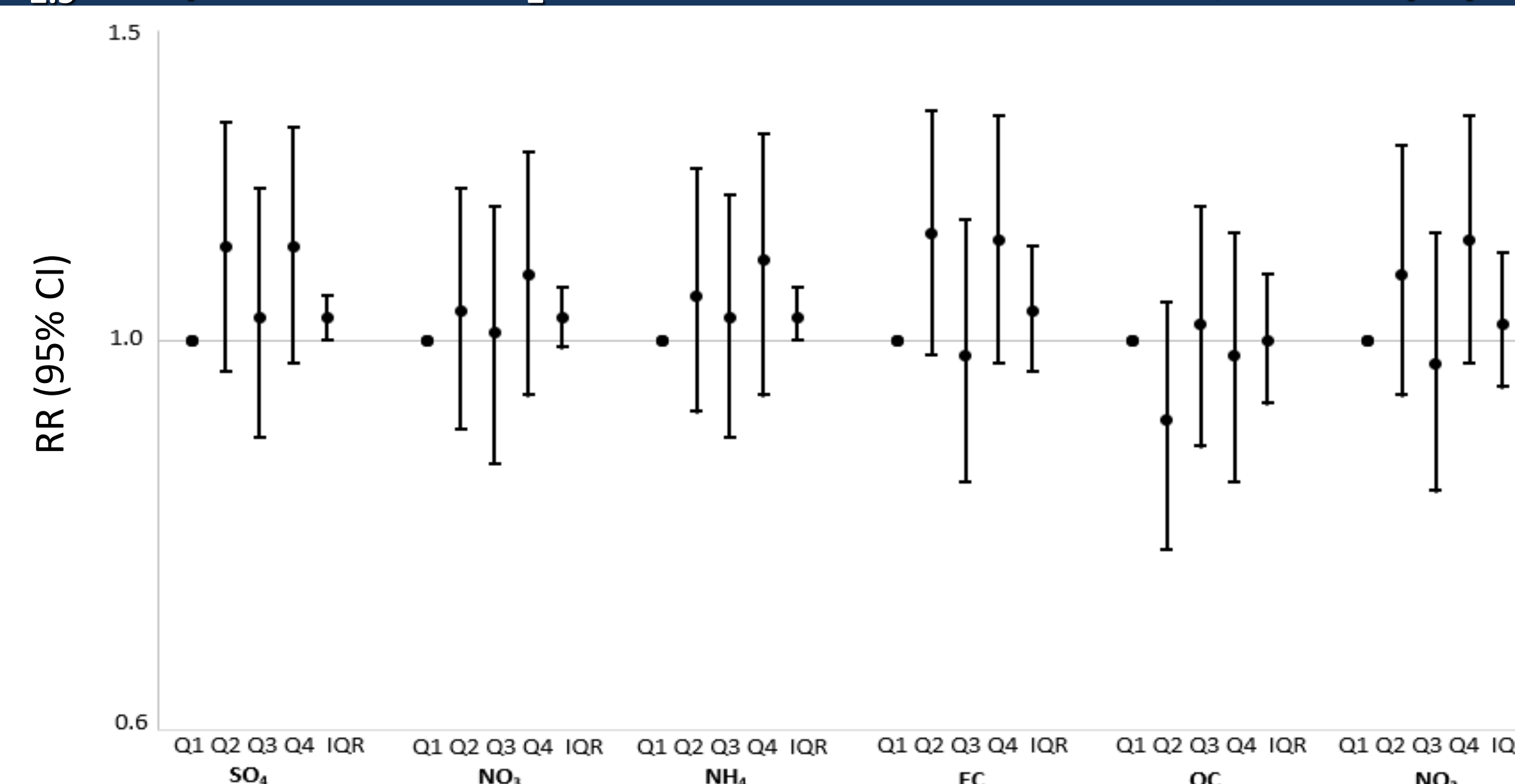
### Population characteristics

	Overall (n=1908)		Premenopausal (n=1325)		Postmenopausal (n=575)	
	N	%	N	%	N	%
<b>Race/Ethnicity</b>						
Non-Hispanic white	1372	72	948	72	420	73
Non-Hispanic Black	355	19	235	18	120	21
Asian, Hispanic, or Other	181	9	142	11	35	6
<b>Highest level of education</b>						
< high school/high school graduate	383	20	278	21	103	18
Vocational/technical school/associate's	290	15	176	13	111	19
College degree or higher	1111	58	794	60	314	55
Other	124	7	77	6	47	8
<b>Cigarette smoking status</b>						
Never	1390	73	1013	76	371	64
Ever	518	27	312	24	204	35
<b>BMI</b>						
<25.0	666	35	521	39	144	25
25.0-<30.0	531	28	339	26	189	33
≥30.0	711	37	465	35	242	42
<b>Age (years) at donation (mean, sd)</b>	41.6	13.8	34.9	10.0	56.9	8.2

### PM<sub>2.5</sub> associations with TDLU count, overall and by menopausal status

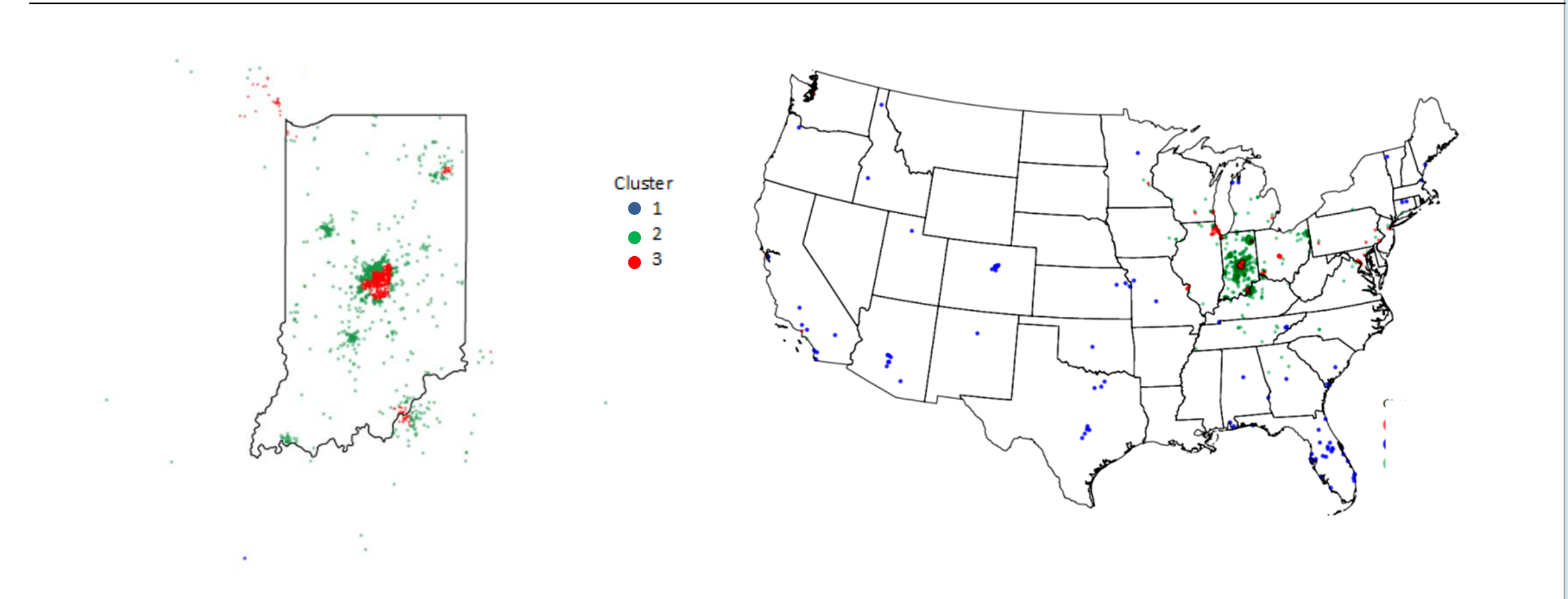


### PM<sub>2.5</sub> component and NO<sub>2</sub> associations with TDLU count, overall population

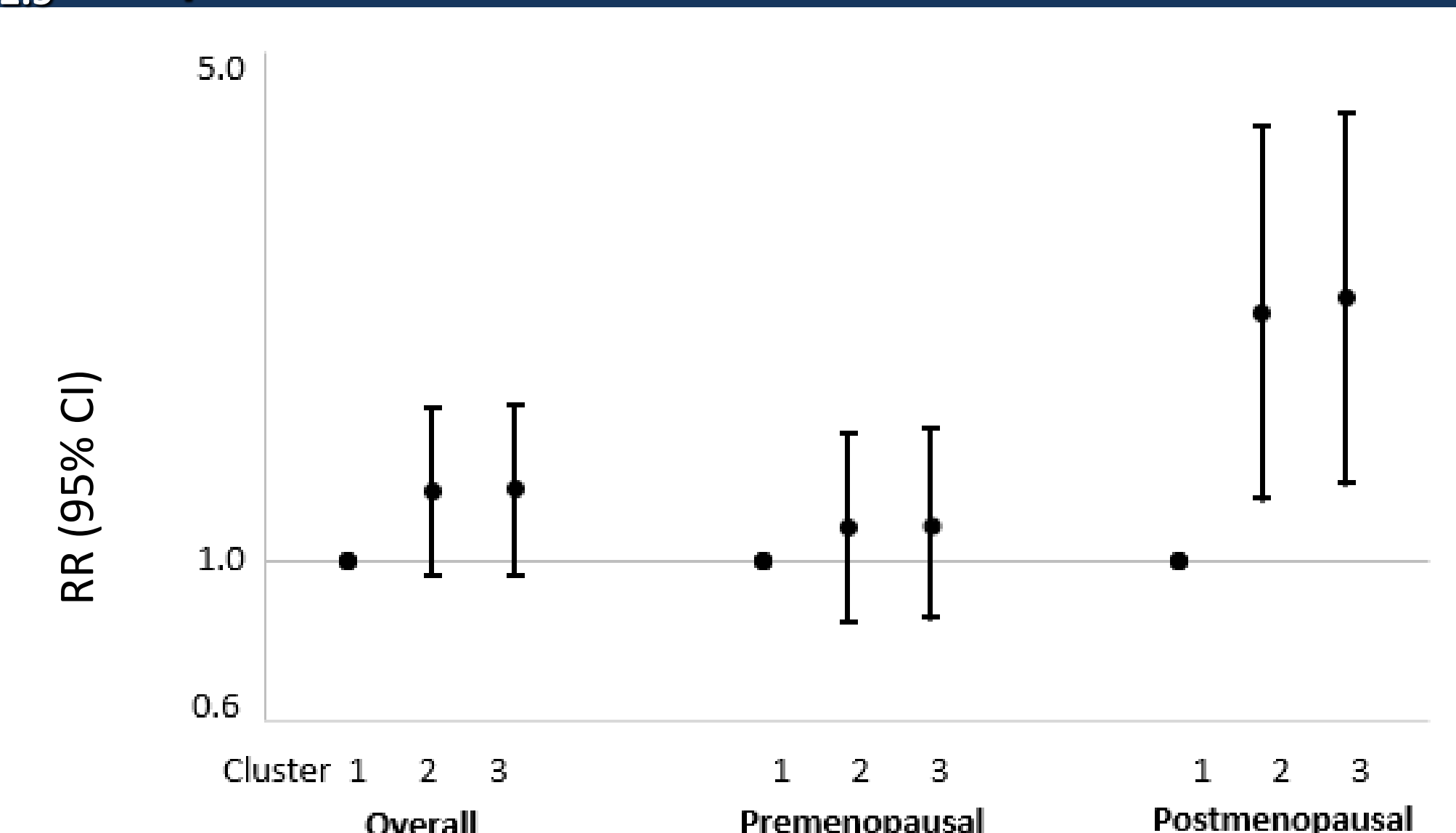


### PM<sub>2.5</sub> component levels and geographic variation by cluster

PM <sub>2.5</sub> components (μg/m <sup>3</sup> )	Overall population (n=1908)		Cluster 1 (n=88)		Cluster 2 (n=958)		Cluster 3 (n=862)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
SO <sub>4</sub>	2.4	0.3	1.4	0.5	2.4	0.2	2.5	0.2
NO <sub>3</sub>	1.9	0.4	0.6	0.4	1.8	0.3	2.1	0.2
NH <sub>4</sub>	1.2	0.2	0.5	0.2	1.2	0.1	1.4	0.1
EC	1.3	0.5	0.8	0.4	1.0	0.3	1.7	0.3
OC	2.0	0.5	1.6	0.7	1.7	0.3	2.4	0.4



### PM<sub>2.5</sub> component cluster associations with TDLU count



## Discussion

Living in areas of higher exposure to PM<sub>2.5</sub> was associated with reduced involution of the breast as measured by TDLU count, particularly among postmenopausal women

Gaseous pollutants, except for the 4<sup>th</sup> quartile of NO<sub>2</sub> with TDLU count, were not associated with measures of TDLU involution

**Limitations:** Potential for nonrepresentative sampling of breast tissue, residential air pollution levels do not fully account for variation in daily activities, potential for measurement error in air pollution estimates

**Strengths:** Large sample, demographically diverse women, use of healthy breast tissue, examined multiple outdoor pollutants and multiple measures of TDLU involution, considered clusters of PM<sub>2.5</sub> profiles

## Acknowledgements

This work was supported by projects Z01-ES044005 and Z1AES103332-01 of the Intramural Research Program of the NIH, NIEHS and NCI. We thank contributors, including Indiana University who collected data used in this study, as well as donors and their families, whose help and participation made this work possible.