The Association of Ambient Air Pollution with Sleep Apnea: The Multi-Ethnic Study of Atherosclerosis

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Abstract

Rationale: Air pollution may influence sleep through airway inflammation or autonomic nervous system pathway alterations. Epidemiological studies may provide evidence of relationships between chronic air pollution exposure and sleep apnea.

Objective: To determine if ambient-derived pollution exposure was associated with obstructive sleep apnea and objective sleep disruption.

Methods: We analyzed data from a sample of the Multi-Ethnic Study of Atherosclerosis who participated in both the Sleep and Air studies. Mean annual and 5-year exposure levels to nitrogen dioxide and $PM_{2.5}$ were estimated at participants' homes using spatio-temporal models based on cohort-specific monitoring. Participants completed in-home full polysomnography and 7 days of wrist actigraphy. Multivariate models, adjusted for demographics, co-morbidities, socio-economic factors and site, assessed if air pollution was associated with sleep apnea (an apnea hypopnea index ≥15) and actigraphy-measured sleep efficiency

Results: Participants (n=1974) were an average age 68 (+/- 9) years, 46% male, 36% white, 24% Hispanic, 28% black and 12% Asian. Of these, 48% had sleep apnea and 25% a sleep efficiency ≤ 88%. A 10 ppb annual increase in nitrogen dioxide exposure was associated with 39% greater adjusted odds of sleep apnea 95% CI (1.03, 1.87). A 5 $\mu g/m^3$ greater annual $PM_{2.5}$ exposure was also associated with 60% greater odds of sleep apnea, 95% CI (0.98, 2.62). Sleep efficiency was not associated with air pollution levels in fully adjusted models.

Conclusions: Individuals with higher annual NO_2 and $PM_{2.5}$ exposure levels had greater odds of sleep apnea. These data suggest that, in addition to individual risk factors, environmental factors also contribute to the variation of sleep disorders across groups, possibly contributing to health disparities.

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Sleep disruption and obstructive sleep apnea (OSA) are associated with hypertension, diabetes, stroke, ischemic heart disease, cancer, and cardiac death.(1-3) Proposed mechanisms include altered autonomic tone, increased inflammation and metabolic dysregulation. Similarly, air pollution has been linked with cerebrovascular disease, cancer and cardiovascular morbidity and overall mortality, attributed in part to an increased systemic inflammatory response to fine particles.(4-7) Ambient air pollution consists of fine particulate matter as well as gaseous products of combustion (oxides of nitrogen), produced through burning fossil fuels from automobiles emissions to power plants. Although there is increasing interest in the influence of the environment on sleep, there is limited research evaluating the relationship between sleep and air pollution.

Few studies have examined epidemiological effects of air pollution on disorders of the upper airway. Epidemiological studies have typically highlighted the consequences of pollution on the distal airways associated with respiratory disease: chronic obstructive lung disease (COPD) and asthma are all worsened by air pollution;(8-11). High levels of pollutions increase the risk of respiratory infections requiring hospitalization in children and mortality in the elderly.(10) Air pollution exposure can impair pulmonary immune defense and alter normal airway clearance by injury and inflammation of airway mucosa.(12) The proximal upper airways such as the naso-pharynx, may respond similarly with inflammation and edema.(13) Thus, air pollution levels may contribute to OSA risk and severity through upper airway irritation, edema and subsequent narrowing. Prior studies have shown some association of short-term

particulate matter (PM_{10}) levels with apnea hypopnea index (AHI) and nocturnal hypoxemia,(14, 15) but were limited by the available air pollution data and lack of racial diversity of the studies.

Air pollution exposures differ geographically and may partially explain difference in lung and sleep health by demographics such as socio-economic status, race and ethnicity. Disadvantaged neighborhoods with low SES residents are often exposed to higher ambient air pollution. In studies in the US and developed countries, a consistent pattern of greater burden of air pollutants was shown to aggregate in lower SES communities.(16) In addition to the upper airway irritation and congestion induced by air pollution, neuro-inflammation and neurotoxicity may also contribute to sleep disruption.(17) Poor air quality may partially explain observations of reduced sleep quality among residents living in low SES neighborhoods, in addition to the effects of poor social cohesion, fear of crime and greater psychosocial stressors.(18-20) Air pollution levels therefore may further contribute to sleep health disparities.

Utilizing a cohort from the Multi-ethnic Study of Atherosclerosis (MESA), subjects participating in the MESA AIR and Sleep studies, we investigated if ambient air pollution levels were associated with sleep apnea and sleep disruption. We hypothesized that greater levels of long-term nitrous oxide and particulate matter pollution would be associated with a higher risk of OSA and lower sleep efficiency. We also hypothesized that short-term particulate matter levels would have a similar association with sleep metrics.

Materials and Methods

Data

The Multi-Ethnic Study of Atherosclerosis (MESA) is a longitudinal study of cardiovascular disease among adults aged 45-84 years. Subjects without clinical cardiovascular disease at baseline were recruited from the community in six United States cities (Los Angeles, CA; New York City, NY; Chicago, IL; Winston-Salem, NC; St. Paul, MN and Baltimore, MD). The current sample was restricted to those with air pollution data who agreed to participate in the MESA Sleep ancillary study that occurred after the 10-year MESA follow-up (Exam 5 in 2010-2013). The institutional review board at each site approved the study and all participants gave written informed consent.

MESA Air

Individual air pollution exposure estimates were calculated from data collected from community and Air Quality System monitoring sites in each metropolitan area, (see online supplement). These data were then integrated with detailed geographical data (including residential location, roadway proximity, population density, vegetative index, industrial pollution sources and land use) using hierarchical spatiotemporal modeling. Details of MESA Air recruitment, exposure assessment and methodology for estimating individual-level long-term air pollution exposure have been previously described.(21) Exposures include one and 5-year

averages prior to sleep study for $PM_{2.5}$, nitrogen dioxide (NO_2) and oxides of nitrogen (NO_x). As NO_x distributions were nearly identical to NO_2, only NO_2 is reported here. Short-term $PM_{2.5}$ levels were collected for day of the study utilizing city-wide air quality monitoring station data. These data were pre-adjusted for city-specific trends by day of week, calendar day, temperature and dew points using splines to account for seasonality and local meteorology.(22)

MESA Sleep

Through the MESA Sleep Ancillary study, a proportion of MESA subjects had sleep assessed via one-week actigraphy and in-home full polysomnography as described previously (see online data supplement). (19, 23) Objective sleep disruption was measured by actigraphy; sleep efficiency (the proportion of time asleep over total time in bed) was calculated from 7-day average of scored actigraphy. The apnea hypopnea index (AHI) was calculated by including all apneas and hypopneas with 4% or greater desaturation or an arousal on polysomnogram divided by total sleep time.

Covariates

Socio-demographic and co-morbidity data were obtained from the MESA health and medical history surveys at the fifth examination (see online supplement). Depressive symptoms were defined as a Center for Epidemiological Studies Depression scale >16.(24) To account for neighborhood SES at the current residence, we utilized census-tract level data from the

American Community Survey 5-year estimates from 2007-2011. We created a measure of census tract SES including > 25 percentile of resident families below poverty, >12% of resident males of 25 years or older unemployed and >30% of residents with less than high school education.

Analysis

We evaluated for differences in the cohort socio-demographics from the parent MESA sample and by air pollution exposure by quartile, using chi-squared for categorical variables and t-tests for continuous variables. We defined OSA as an AHI ≥ 15, a threshold considered moderate to severe.(25) We compared those with OSA to those without by sample characteristics. We defined reduced sleep efficiency as ≤88%, corresponding to the lowest 25% percentile of the 7-day actigraphy average, given that its distribution was not normal, highly skewed and to improve interpretability.

We examined associations of OSA and reduced sleep efficiency with long-term exposure to ambient air pollution (nitrogen dioxide and $PM_{2.5}$ exposures averaged over 1 and 5-years prior to sleep evaluation) and short-term $PM_{2.5}$ in multi-variate logistic regression. For interpretability, we modeled NO_2 in units of 10 ppb and $PM_{2.5}$ by 5μg/m^3; we excluded observations with any missing covariates. The simplest model adjusted for age, sex, and BMI, (plus OSA in the sleep efficiency analysis). Model two added the co-variates of individual household income, race/ethnicity, diabetes, hypertension, short sleep duration (in actigraphy

outcome only), smoking status, and neighborhood SES features. These covariates were included as they differed by air pollution and/or sleep apnea. Model three added adjustment for site.

We performed several additional sensitivity analyses to assess the strength of our findings. We evaluated the association of AHI ≥ 15 using the 4% oxygen desaturation definition of hypopnea (Centers for Medicare and Medicaid criteria) with air pollution. We evaluated if including use of medications for reflux and evidence of airflow obstruction on spirometry changed the observed associations. We also performed analyses excluding those with mild OSA (AHI 5-15).

In exploratory analysis, we assessed AHI, modeled continuously, in generalized linear models. These models included the same units of air pollution predictors and covariates as the logistic regression models. Site, residential SES and race/ethnicity had high collinearity with air pollution levels (and with each other) precluding assessment of their potential effect modification with one another. We also explored the association of air pollution with sleep apnea when stratified by site.

Results

Of the 1,974 MESA subjects with both sleep polysomnography data and air pollution data (figure 1), the mean age was 68.4 years (+/- 9.2) and BMI was 28.7 kg/m^2 (+/- 5.6) with

racial/ethnic, socio-economic and geographic diversity (table 1a). The cohort had greater racial/ethnic diversity but otherwise did not differ significantly from the parent MESA study population by demographics. Air pollution differed substantially by site, with the highest levels and greatest distribution in New York and Los Angeles, lowest in St. Paul and Winston-Salem areas. Pollution levels also differed significantly by race/ethnicity, education level, income level, and neighborhood SES with higher pollution exposure levels observed in minorities, those with high school or less education, lower household income and those living in lower SES neighborhoods.

The median AHI was 14.4 (IQR 7.1-27.4), (table 1b). Those with OSA were, as expected, more often men, obese, former or current smokers, hypertensive, and diabetic but did not differ by income level, education level or residential SES features. OSA was more often identified in those tested in the spring and summer months (April-September). Median NO_2 exposure estimates averaged over 5 years was 14.8 ppb (IQR 10, 23.7) and were well below the EPA National Ambient Air Quality Standards standard of <53 ppb (https://www.epa.gov/criteria-air-pollutants/naaqs-table). In contrast, the median $PM_{2.5}$ exposure estimate over 5-years was 12.3µg/m^3 (IQR 11.5, 13.5), above the EPA standard of 12.0 µg/m^3.

Sleep and Oxides of Nitrogen: NO_2

There was an association of NO_2 exposure with OSA in fully adjusted models including site

(table 2a), but not in the simpler models. Ten ppb greater NO_2 (averaged over either one or five year) was associated with a nearly 40% greater odds of OSA, 95% CI (1.03, 1.87), figure 2. The association was seen but not significant when using the 4% desaturation criteria for hypopneas (Centers for Medicare and Medicaid Services definition) for AHI, (online *data supplement table* E1). There was not an association seen with AHI modeled continuously (table E2). When stratified by site, associations persisted only in sites with greater pollution exposure and variation (Los Angeles and New York City), (table E3).

A ten ppb greater NO_2 exposure was associated with 19% greater odds of a low sleep efficiency (table 2b), in minimally adjusted models. With social and residential factors included in the model, the association was no longer significant.

Sleep and Particulate Matter: $PM_{2.5}$

An association was observed between one-year average $PM_{2.5}$ exposure estimates with OSA, but not with 5-year average $PM_{2.5}$ exposure estimates. In fully adjusted models, each increase in 5 $\mu g/m^3$ of annual mean $PM_{2.5}$ exposure was associated with 60% greater odds of OSA (95% CI 0.98, 2.62), figure 2. This was significant when site was not in the model with a narrower confidence interval (table 3a). Short-term $PM_{2.5}$ levels were not associated with OSA in logistic regression. Using the CMS hypopnea definition (4% oxygen desaturation), each 5 $\mu g/m^3$ greater annual $PM_{2.5}$ exposure was associated with 59% greater odds of CMS AHI ≥15 OSA (table E1). With AHI modeled continuously, there was evidence of association only in the

minimally adjusted model (table E2). When stratified by site, only the Los Angeles site demonstrated a clear association of $PM_{2.5}$ exposure to sleep apnea (table E3).

For 5-year average $PM_{2.5}$ exposure, each 5 $\mu g/m^3$ was associated with 51% greater odds of reduced sleep efficiency, 95% CI (1.09, 2.09) in the age, sex, BMI and OSA only adjusted model. However, there was no evidence of association after adjustment for individual socio-demographics and residential SES (table 3b). One-year $PM_{2.5}$ exposure levels and short-term $PM_{2.5}$ levels were not associated with sleep efficiency.

Sensitivity Analyses

Including use of proton pump inhibitors in the models did not change the association of air pollution with sleep apnea. We also found no difference when spirometry data was included (available in only a subset of the cohort n=1407). When those with mild OSA were excluded (AHI 5-15; n=719), association of OSA with air pollutions remained robust; the odds ratio for NO_2 was 1.52, 95% CI (1.09, 2.12) and for $PM_{2.5}$ was 1.65 95% CI (0.97, 2.81), in fully adjusted models.

Discussion

This study reveals an association of chronic exposure to ambient derived air pollution with sleep apnea. Higher average yearly levels of NO_2 and $PM_{2.5}$ were associated with increased odds

of moderate to severe sleep apnea, independent of race/ethnicity, income, diabetes, hypertension, neighborhood SES and site. The cumulative effects of air pollution exposure over the year may lead to changes to the upper airway. However, $PM_{2.5}$ exposure averaged over five-years was not associated with sleep apnea, possibly due to chronic adaptations. Exposure to greater average NO_2 and $PM_{2.5}$ levels were less robustly associated with lower sleep efficiency. This association attenuated after adjusting for co-morbidities, individual demographics, and residential factors, all known to contribute to sleep quality.(19, 23)

There are several potential mechanisms linking air pollution to sleep. Experimental models in mammals demonstrate that ambient air pollutants cause upper airway edema, inflammation and irritation (26, 27) which may contribute to upper airway obstruction during sleep. Fine particulate material and oxides of nitrogen are associated with chronic rhinosinusitis, non-allergic and allergic rhinitis (26, 28), and excess risk of upper respiratory infections (29, 30). However, most data originate in regions with much higher pollution exposure levels than in this study. $PM_{2.5}$ has been shown in vivo to induce inflammatory response in human nasal epithelial cells.(31) These ambient pollutants are also known to contribute to incident obstructive airway disease and respiratory symptoms in the elderly;(32) this may be another mechanism contributing to sleep disordered breathing. Chronic upper airway irritation and inflammation from to air pollution may induce adenoid and tonsillar hypertrophy and consequently upper airway narrowing. Further experimental studies are needed to verify these hypotheses. Fine particulate matter and traffic–related air pollutants

represented by oxides of nitrogen may directly penetrate the central nervous system causing neurotoxicity and neuro-inflammation,(17) which may affect brain areas involved in the regulation of sleep and control of ventilation. Long-term air pollution exposure has been associated with cognitive impairment, neuro-inflammation and neurodegeneration.(17)

Environmental factors in the form of air pollution may increase the risk of OSA and may therefore contribute to sleep health disparities. Prior environmental studies of sleep have predominantly focused on features of the social environment such as low social cohesion, crowding and neighborhood disorder(19, 33, 34) as explanatory factors contributing to poor sleep in low SES neighborhoods and sleep disparities. More recently, the built environment and neighborhood walkability features have been associated with sleep apnea.(35) Neighborhood disadvantage, as quantified by census-track indicators of poverty, low education attainment, and family structure, has been associated with an increased risk of sleep apnea in children,(36-38) but not yet in adults. These pediatric studies postulated that geographic differences in sleep disorders may relate to air quality, but did not have data to address this hypothesis.

Our results are consistent with the few prior studies evaluating air pollution and sleep. A Swiss study found an association of sleep disturbance, measured by electrocardiogram features, with proximity to roadways.(39) Using Sleep Heart Health Study data, Zanobetti *et al* reported an association of short-term PM_{10} with an elevation in AHI and reduced sleep efficiency particularly in the summer.(15) Greater air pollution (NO_2 and $PM_{2.5}$) exposure in Taiwan was also associated with greater AHI and oxygen desaturation index, with a similar

seasonal component of spring and winter.(40) Elevated short-term ozone and temperature were associated with a higher AHI in a European study.(41) Several studies also have reported associations with meteorological conditions such as temperature and humidity.(42) These studies reported strong seasonal variation, perhaps reflecting an interaction of pollution with air temperature, environmental allergens such as pollens and humidity levels. We found a seasonal variation in AHI but no interaction with the association of long-term air pollution exposure and sleep apnea. Our study utilized year-long averages in multiple geographical locations with state of the art modeling to minimize the effect of these regional and temporal variations on pollution.

We observed differences in associations of air pollution with our sleep outcomes depending on exposure durations (daily, annual, five-year). Whether this relates to differences in the biological effects of different exposures or relates to measurement issues is not clear. The lack of clear associations of sleep apnea with 5-year average and short-term $PM_{2.5}$ exposure may be a falsely null hypothesis due to overall high prevalence of OSA, the lack of air pollution variation within cities and overall low burden of ambient air pollution exposures compared to other urban environments worldwide(43) or to other measurement issues. For example, short-term exposures were city-wide measures as individual-level estimates were not possible. The null findings for short-term exposure estimates also may reflect the importance of longer-term exposures causing chronic changes in the airway, brain or other tissues. The stronger association between one-year $PM_{2.5}$ compared to 5-year $PM_{2.5}$ exposure estimates similarly

may reflect to more airway adaptations with chronic higher pollution exposure over 5-years.

Our primary outcome was based on OSA defined using the more sensitive American Academy of Sleep Medicine (AASM) definition of hypopnea (44) rather than the strict ≥4% oxygen desaturation hypopnea criterion specified by the Centers for Medicaid and Medicare services (CMS). The CMS AHI has been criticized as it may under-diagnose in women and non-obese individuals, who are less likely to experience deep desaturations with events.(45) When using the more stringent definition of hypopneas (≥4% desaturation) we observed similar associations for $PM_{2.5}$ but less significant associations for NO_2 perhaps reflecting distinct impact of these pollutants on the airway – one leading to more desaturation while the other contributing to arousals. This is consistent with the finding of association of lower sleep efficiency with higher NO_2 exposure levels. These differences may reflect the more subtle pathological effects of air pollution on the upper airway detectable only in the more sensitive AASM definition of hypopnea.

The strengths of this study include the detailed individual air pollution metrics with spatiotemporal modeling, the diversity of the subjects (both in racial/ethnic background and geography), the large sample size gathered from the community, and the use of objective sleep measures. The limitations of the study include the observational nature of the study and assessment of sleep at only one time point, limiting evaluation of causality and a full understanding of how exposure durations influence sleep. Pollution exposure differed substantially by site, with low exposures in some areas, making it difficult to separate site from

pollution effects. Site was also highly co-linear with other socio-demographic features (race/ethnicity, SES). In addition, the MESA participants in our cohort were older, with a mean age of 68.5 years; our findings may not be generalizable to younger individuals. Although our sample was diverse, there was inadequate power to test for race differences. We adjusted for many measured potential confounders, but other factors, including environmental features associated with air pollution, such as noise and light pollution, may explain the observed relationship with sleep disruption. Noise from traffic is also a known sleep disruptor and has been associated with cortical arousals, sleep fragmentation, insomnia and self-reported poor sleep.(46) Traffic noise rather than traffic-associated pollution (NO_2) may explain some of our observed associations, although relationships remained robust in sensitivity models adjusting for road proximity. Urban living has additional sleep disruptors such as light pollution,(47) which can impact circadian rhythm, melatonin excretion and result in sleep onset delay and fragmentation.

While prior studies have largely focused on individual risk factors for sleep apnea, these data suggest environmental features also contribute to the variation of sleep disorders across groups. This has implications for regulatory standards, public health, environmental justice and health disparities, as higher levels of air pollution are more prevalent in poor, urban areas as seen in this MESA cohort.(48) Populations residing in cities with ambient air pollution above WHO levels may have a greater risk of sleep apnea and sleep disruption, in addition to the other known effects of air pollution on mortality, cardiovascular, pulmonary, and

neurodegenerative diseases and cancer risk.(43, 49-51) Efforts to improve air quality could improve sleep health, decreasing the prevalence and severity of sleep apnea potentially. Furthermore, air quality improvements may reduce sleep health disparities as the poor may be particularly susceptible to air pollution, with less access to protection indoors, lacking air conditioners, air filtration systems, relying on open windows and having greater occupational exposure to the outdoors.

Conclusions

This study demonstrates an association of ambient air pollution exposure with sleep apnea. Chronic exposure to greater levels of air pollution may adversely influence breathing during sleep, suggesting possible etiologies of sleep health disparities. Future studies are needed to discern the effects of specific air pollutants from other neighborhood and regional features, to explore possible mechanisms, and to evaluate if improving air quality improves sleep health.

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Figure Legends:

Figure 1: Flow chart detailing the sample included in this analysis from the parent MESA cohort.

Figure 2: Adjusted odds of OSA (AHI≥15) with ambient air pollution, NO2 (in 10 ppb units) and PM2.5 (in 5 μg/m3 units) exposure estimates averaged over one year and 5 years prior to sleep assessment; odds ratio and 95% confidence intervals shown. Logistic regression models adjusted for age, sex, BMI, diabetes, hypertension, race/ethnicity, household income, smoking status, residential SES and site.

Table 1a: MESA Sleep and Air pollution sample characteristics (n= 1974)

	Total % (n) N=1974
Age (years) * mean (SD)	68.4 (9.2)
% Men (n) *	45.9 (905)
BMI (kg/m^2) * mean (SD)	28.7 (5.6)
% Married (n) †	60.5 (1,176)
% Smoker (former/current) (n) *†	45.2 (886)
% Depressed (CES-D>16) (n) †	14.4 (279)
% Hypertension *†	57.5 (1,134)
% Diabetic *†	39.9 (780)
% Race/Ethnicity (n) *†	
White	35.9 (708)
Chinese-American	12.2 (240)
African-American	28.0 (553)
Hispanic	24.0 (473)
Total Family Income ($) †	**n**
< 20,000	20.6 (394)
20-49,999	33.8 (647)
50,000-99,999	27.5 (528)
≥ 100,000	18.2 (348)
Education Level †	**n**
High School or less	31.6 (622)
Some college/technical/associate	29.1 (574)
Bachelor degree or more	39.3 (774)
Site *†	**n**
Winston-Salem, NC (Wake Forest)	14.7 (291)
New York City, NY (Columbia)	17.9 (354)
Baltimore, MD (JHU)	14.6 (289)
St. Paul, MN (UMN)	17.1 (338)
Chicago, IL (NWU)	18.9 (373)
Los Angeles, CA (UCLA)	16.7 (329)
Census-tract SES †	**Median (IQR)**
% Unemployed males >25 yrs old	**6 (3, 10)**
% households below poverty	11 (6, 20)
% professional occupation	34 (23, 50)
% less than high school education	19 (10, 32)
Census tract LOW SES Composite †	**% n**
% Low SES neighborhood (n)	34.7 (685)

*Significant difference by OSA (AHI ≥ 15 vs. <15), p<0.05 † Significant difference by NO_2 quartile

Table 1b: MESA Sleep and Air pollution sample characteristics (n= 1974) presented as median and intra-quartile range (IQR)

Sleep Metrics: PSG Data	**median**	**IQR**
AHI (AASM criterion) events/hr	14.4	7.1, 27.2
AHI (4% desaturation) events/hr	9.1	3.2, 19.7
4% ODI events/hr *	8.2	3.2, 19.2
Nadir saturation *	85	80, 89
% sleep time with <90% saturation	0.63	0.04, 3.32
% OSA (AHI > 15 by AASM) (n) *	48.0%	N=884
Sleep Metrics: Actigraphy Data		
% WASO > 60 min (n) *	10.8%	N=201
% Short sleeper (< 6hrs) (n) *	31%	N=578
Sleep efficiency over 7 days *	90.5	88.0, 92.5
Sleep time over 7 days (hrs)*	6.64	5.74, 7.38
Air pollution levels	**median**	**IQR**
5-year NO_2 (ppb)	14.8	10.0, 23.7
1-year NO_2 (ppb)	13.0	9.0, 21.4
1-year $PM_{2.5}$ ($\mu g/m^3$)*	11.0	10.3, 12.0
5-year $PM_{2.5}$ ($\mu g/m^3$)	12.3	11.5, 13.5

*Significant difference by OSA (AHI > 15 vs. ≤ 15), $p<0.05$

Table 2: NO_2 average exposure estimates (in 10 ppb units), over 1 to 5 years prior to sleep assessment, presented as odds ratios (95% Confidence Interval).

2A: Outcome of sleep apnea (AHI>15 on PSG) *

	Model 1	**Model 2**	**Model 3**
One-year	N=1961	N=1884	N=1884
NO_2 (per 10 ppb)	1.05 (0.95, 1.16)	1.00 (0.88, 1.14)	*1.39 (1.03, 1.87)* ‡
Five-year	N=1948	N=1871	*N=1871*
NO_2 (per 10 ppb)	1.06 (0.96, 1.17)	1.01 (0.89, 1.15)	*1.41 (1.04, 1.92)* ‡

*Adjusting for age, sex, BMI (**model 1**); plus diabetes, hypertension, race/ethnicity, household income, smoking status, and residential SES (**model 2**); plus site (**model 3)**

2B: Outcome of reduced sleep efficiency (≤88% on actigraphy) †

	Model 1	**Model 2**	**Model 3**
1yr prior	N=1854	N=1781	N=1781
NO_2 (per 10 ppb)	*1.19 (1.07, 1.33)* ‡	1.11 (0.96, 1.28)§	1.04 (0.74, 1.44)
5yr prior	N=1842	N=1769	n=1769
NO_2 (per 10 ppb)	*1.19 (1.07, 1.33)* ‡	1.12 (0.97, 1.29)§	1.09 (0.77, 1.53)

†Adjusted for age, sex, BMI, OSA (AHI≥15) (**model 1**); plus race/ethnicity, income, smoking status, diabetes, hypertension, short sleep duration (< 6 hours), and residential SES (**model 2**); plus site (**model 3)**

‡$p< 0.05$, § $p<0.10$

Table 3: $PM_{2.5}$ exposure estimates (in 5 μg/m^3 units), averaged over 1 to 5 years prior to sleep assessment, presented as odds ratio (95% Confidence Interval).
3A: Outcome sleep apnea (AHI > 15)

Long-term $PM_{2.5}$	**Model 1**	**Model 2**	**Model 3**
$PM_{2.5}$ 1 yr	*N=1928*	*N=1853*	*N=1853*
per 5 ug/m^3 $PM_{2.5}$	*1.79 (1.25, 2.55)* ‡	*1.63 (1.09, 2.44)* ‡	*1.60 (0.98, 2.62)* §
$PM_{2.5}$ 5yr	N=1950	N=1873	N=1873
per 5 ug/m^3 $PM_{2.5}$	1.24 (0.93, 1.65)	1.14 (0.82, 1.58)	1.31 (0.78, 2.20)
Short-term $PM_{2.5}$	N=1916	N=1812	N=1812
$PM_{2.5}$ day prior*	1.00 (0.98, 1.02)	1.01 (0.98, 1.03)	1.01 (0.99, 1.03)
$PM_{2.5}$ day of PSG*	1.00 (0.98, 1.02)	0.99 (0.97, 1.02)	0.99 (0.97, 1.02)

*Adjusted for age, sex, BMI (**model 1**); plus diabetes, hypertension, race/ethnicity, household income, smoking status, residential SES (**model 2**); plus site (**model 3**)

3B: Outcome reduced sleep efficiency (*≤ 88% on actigraphy*)†

	Model 1	**Model 2**	**Model 3**
$PM_{2.5}$ 1yr prior	N=1822	N=1750	N=1750
per 5 ug/m^3 $PM_{2.5}$	1.34 (0.91, 1.98)	1.00 (0.63, 1.58)	0.92 (0.53, 1.60)
$PM_{2.5}$ 5yr prior	N=1843	N=1770	N=1770
per 5 ug/m^3 $PM_{2.5}$	*1.51 (1.09, 2.09)* ‡	1.28 (0.88, 1.87)	1.07 (0.59, 1.93)
Short-term $PM_{2.5}$	N=1811	N=1711	
$PM_{2.5}$ day prior*	1.00 (0.98, 1.02)	1.01 (0.98, 1.04)	1.01 (0.98, 1.04)
$PM_{2.5}$ day of PSG*	1.01 (0.98, 1.03)	0.99 (0.97, 1.02)	1.01 (0.98, 1.03)

† Adjusting for age, sex, BMI, OSA (AHI≥15) (**model 1**); model 1 plus race/ethnicity, income, smoking status, diabetes, hypertension, short sleep duration (< 6 hours) and residential SES (**model 2);** model 2 plus site (**model 3**)

*Short term $PM_{2.5}$ are city-wide levels from day of and day prior to overnight polysomnography. The values have been pre-adjusted for seasonal and meteorological trends

‡$p< 0.05$, § $p<0.10$

Figure

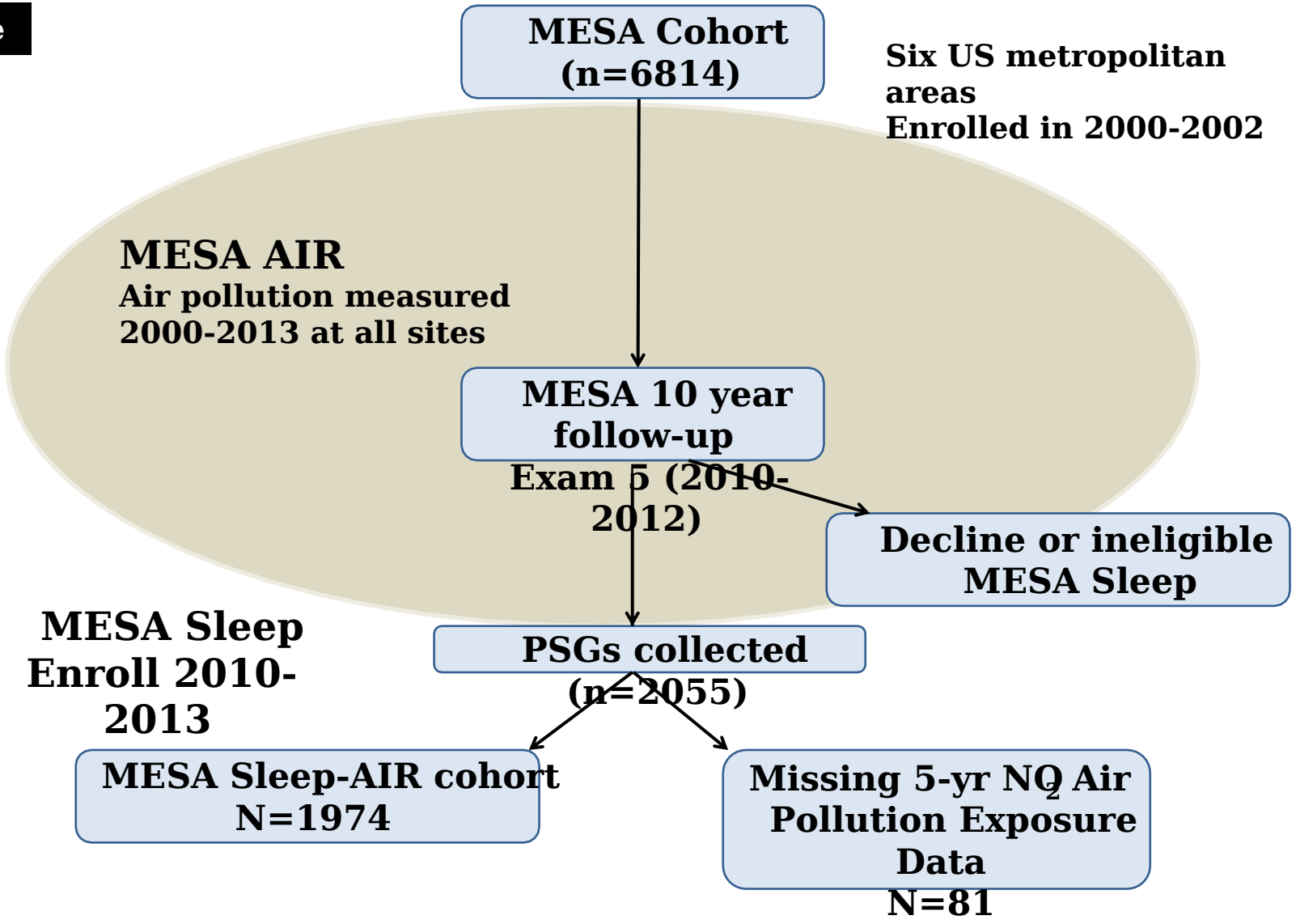
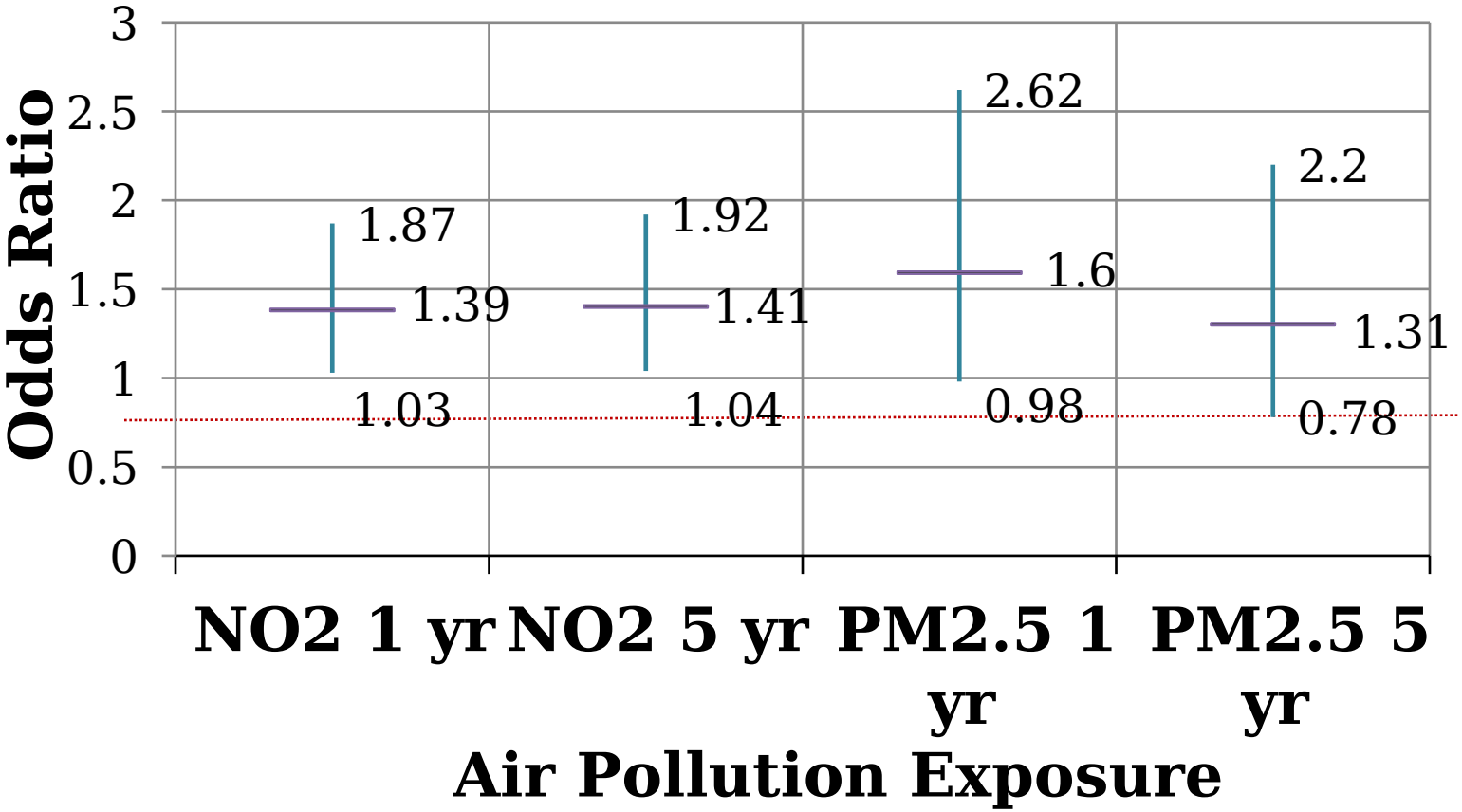

MESA Cohort (n=6814)
Six US metropolitan areas
Enrolled in 2000-2002
MESA AIR
Air pollution measured 2000-2013 at all sites
MESA 10 year follow-up
Exam 5 (2010-2012)
Decline or ineligible MESA Sleep
MESA Sleep Enroll 2010-2013
PSGs collected (n=2055)
MESA Sleep-AIR cohort N=1974
Missing 5-yr NO2 Air Pollution Exposure Data N=81

Figure 2: Adjusted Odds Ratios for air pollution exposures association with OSA (AHI>15)



Online Data Supplement

The Association of Ambient Air Pollution with Sleep Apnea: The Multi-Ethnic Study of Atherosclerosis

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Methods

MESA AIR: In brief, ambient-source air pollution was assessed by utilizing Environmental Protection Agency operated Air Quality System (AQS) monitors and by deploying more than 7,420 monitors throughout the six MESA metropolitan areas, including some participants' homes. The pollution measurements were integrated with geographical features including residential location, roadway proximity, population density, vegetative index, industrial pollution sources and land use. Dispersion modeling incorporated seasonal and meteorological trends. Participants reported their addresses and estimates were made reflecting time spent at each location if moves occurred in the interval.

MESA SLEEP: Eligible MESA subjects not using positive airway pressure, an oral appliance or home oxygen; ineligible n= 147) were invited to participate and 60% agreed (n=2055). Subjects wore an Actiwatch Spectrum actigraph (Philips Respironics, Murrysville, PA) on their non-dominant wrist for one week and underwent one night in-home full polysomnography with a 15-channel device (Somte System; Compumedics Ltd.). Polysomnography and actigraphy studies were scored by a central Sleep Reading Center by certified polysomnologists, blinded to other data. Sleep/wake status for each 30 second epoch of actigraphy data was computed using the Actiware-Sleep v. 5.59 scoring algorithm. Sleep periods were identified by technicians using sleep diaries, light levels, event markers, and activity levels. Sleep efficiency was time spent in sleep over total time in bed, averaged over the 7-day actigraphy recording.

MESA: Subjects reported race/ethnicity (White non-Hispanic, Black non-Hispanic, Hispanic and Chinese), cigarette smoking status (never, current/former), education level (categorized as high school or less, some college/associate degree, college degree or more) and household income (categorized as < $ 25,000, $25-75,000, > $75,000). Measured weight and height were used to calculate BMI category (<25, 25-29.9, 30-40, >40 kg/m^2) at Exam 5.

Results

Supplemental table E1: Association of NO_2 and $PM_{2.5}$ exposure levels for year prior to PSG using multi-variate logistic regression for outcome of CMS AHI≥15 (only 4% desaturation hypopneas), presented as odds ratio (95% CI).

	Model 1	**Model 2**	**Model 3**
Annual	N=1983	N=1906	N=1906
NO_2 (per 10 ppb)	1.04 (0.94, 1.15)	0.991 (0.86, 1.14)	1.24 (0.90, 1.71)
	N=1948	N=1873	N=1873
$PM_{2.5}$ (per 5 μg/m^3)	1.86 (1.28, 2.69) ‡	1.61 (1.06, 2.46) ‡	1.59 (0.94, 1.27) §

Supplemental table E2: Association of NO_2 and $PM_{2.5}$ exposure levels for year prior to PSG with apnea hypopnea index (AHI) outcome, using generalized linear models, presented as beta (95% CI).

	Model 1	**Model 2**	**Model 3**
One year prior	N=1961	N=1884	N=1884
NO_2 (per 10 ppb)	-0.22 (-0.89, 0.46)	-0.48 (-1.10, 0.13)	0.50 (-.1.25, 2.24)
	N=1928	N=1853	N=1853
$PM_{2.5}$ (per 5μg/m^3)	2.33 (0.35, 4.31) ‡	1.30 (-0.84, 3.44)	1.22 (-1.34, 3.79)

Adjusting for age, sex, BMI (**model 1**); plus race/ethnicity, hypertension, diabetes, smoking status, household income, and residential SES (**model 2**), and for site (**model 3**);

‡$p< 0.05$, § $p<0.10$

Supplemental table E3: Stratified by site: Association of NO_2 and $PM_{2.5}$ exposure levels for year prior to PSG with OSA (AHI≥15), using logistic regression, presented as odds ratio, (95% CI).

Site	**NO_2 (per 10 ppb)**	**$PM_{2.5}$ (per 5μg/m³)**
Winston-Salem, NC n=275	1.07 (0.19, 6.15)	0.57 (0.01, 35.18)
NYC, NY N=342	1.57 (0.99, 2.47) §	1.72 (0.74, 4.00)
Baltimore, MD n=267	0.68 (0.27, 1.68)	0.51 (0.11, 2.52)
Minneapolis, MN, n=317	1.39 (0.41, 4.69)	1.57 (0.41, 6.05)
Chicago, IL n=352	1.72 (0.66, 4.48)	2.58 (0.59, 11.18)
Los Angeles, CA n=320	2.89 (1.13, 7.43) ‡	4.15 (0.95, 18.11) §

Adjusting for age, sex, BMI, race/ethnicity, hypertension, diabetes, smoking status, household income, and residential SES.

‡$p< 0.05$, § $p<0.10$