1. **Full Title:** Ambient Particles and Sleep Health
   
   **Abbreviated Title:** Particles and Sleep Health

2. **Lead Author:** Brent Coull

3. **Timeline:** January 1, 2008 to January 1, 2009

4. **Rationale**

   Obstructive sleep apnea is characterized by loud snoring and disrupted breathing during sleep. There is increasing evidence that such sleep-disordered breathing may increase risk for cardiovascular diseases, including coronary artery disease and stroke, and for hypertension and may reduce quality of life. For instance, the relative risks of cerebrovascular accidents, ischemic heart disease and myocardial infarction range from 1.5 to 4 in snorers as compared to non-snorers (Quan et al, 1997). The physiological conditions associated with sleep-disordered breathing, including hypoxemia, severe hypertension, tachycardia, fragmentation of sleep, arrhythmias, provide biologically plausible explanations for such associations between sleep apnea and cardiovascular morbidity. The increased risk of cardiovascular events shortly after awakening has been linked to sympathetic discharge associated with arousal, which can occur dozens of times each night in patients with sleep apnea.

   At the same time, airborne particulate matter (PM) has consistently been shown to impact cardiovascular health (Brook et al. 2004). Findings from recent studies suggest that autonomic function and systemic inflammation may be two important biological pathways of exposure. Due to the fact that autonomic function is a potentially important biologic pathway in both sleep-disordered breathing and a possible mechanism of PM exposure, it is plausible that PM exposure may be associated with obstructive sleep apnea. To our knowledge, this has never been explored, with the exception of a current investigation conducted by our group on a sample of 48 individuals from a potentially vulnerable population of patients recovering from a recent cardiac event of sufficient magnitude to require hospitalization and cardiac catheterization, collected as part of the Program Project Grant, “Ambient Particles and Cardiac Vulnerability in Humans” (PI:
Gold). Spilsbury et al. (2006) noted that neighborhood disadvantage is a risk factor for pediatric obstructive sleep apnea. These authors concluded that more work is needed to assess the role of environmental factors, including pollution exposures and neighborhood distress, on sleep health. Based on these potentially common biologic mechanisms and existing findings, we propose a project investigating relationships between ambient particle exposures and sleep health in individuals followed as part of the Sleep Heart Health Study (SHHS). For each subject in the SHHS, the plan is to match the nighttime or 24 hour particulate levels recorded on the date of his or her polysomnographic indices, so that the basis of analysis will associate (cross-sectionally) night-to-night changes in pollution to the sleep outcomes recorded.

5. Hypotheses: We propose to use the data collected by the SHHS to test the following hypotheses:

   H1. There exists an association between polysomnographic indices of disturbed sleep/sleep-disturbed breathing and ambient PM$_{2.5}$ levels in the longitudinal cohort of 6400 persons in the SHHS.

   H2. There exists an association between ambient PM$_{2.5}$ levels and subjective sleep quality as measured as part of the larger SHHS Sleep Habits Questionnaire.

6. Data: For H1, we propose to focus on the longitudinal cohort of 6400 persons in the SHHS. SHHS outcomes to be investigated in this aim include the apnea/hypopnea index (AHI), percent sleep time in apnea (obstructive or central), percent sleep time in hypopnea, percent time in desaturation, arousal index, and sleep efficiency.

   For H2, SHHS data used will be subjective sleep quality data collected as part of the Sleep Habits Questionnaire, including difficulty falling asleep, frequent awakenings, and early morning awakenings.

7. Type of Study: This study will be a secondary study in that it deals with non-primary hypotheses of SHHS and with data collected at all investigative centers.

8. Type of Publication: We propose disseminating the results of this investigation in a journal article.

9. Analysis Responsibility: All analyses will be conducted by the study team of Drs. Coull, Gold, and Redline.

10. Introduction

The proposed project represents collaboration between members of the Environmental Statistics Program in the Department of Biostatistics at the Harvard School of Public Health (HSPH) (Coull), the Exposure, Epidemiology and Risk Program in the Department of Environmental Health at HSPH (Gold), and the Division of Clinical Epidemiology at Case Western Reserve University (Redline). The investigators have a well-established working relationship. Dr. Coull is currently the principal investigator (PI) of the Data Management and Environmental Statistics
Core of the National Institutes of Health (NIH) Program Project Grant (PPG) “Ambient Particles and Cardiac Vulnerability in Humans”, on which Dr. Gold is the overall PI and Dr. Redline is the chair of the external advisory committee. These three investigators also collaborate on the analysis of the sleep apnea data from this PPG.

Early analyses from these preliminary data suggest there are associations between thirty-minute averages of oxygen (O2) saturation during sleep and particulate matter less than 2.5 microns (PM2.5) levels during the previous 24 hours [change in O2 sat of -0.132%, 95% CI: (-.261%,-.003%), per 10 µg/m³ increase in PM2.5]. Further, in our preliminary analysis of the PPG sleep data, although we observe negative associations between oxygen (O2) saturation and PM2.5 levels when we consider exposure averaged over the previous day or previous several days, we observe positive associations when we consider very short term exposures within a night. This raises the question of whether this pattern arises due to complex temporal confounding mechanism, perhaps due to sleep state changing within a night. Alternatively, we have to be open to the possibility that pollution can be acting via competing mechanisms, as has been established for other exposures such as nicotine. For instance, pollution could be associated with upper airway inflammation resulting in hypopnea and airway obstruction, but also with neurologic stimulation, which serves to increase arousal and disturbed sleep.

11. Brief Analysis Plan

The HSPH Investigators will work with Dr. Redline, Principal Investigator of the Polysomnographic (PSG) Reading Center of the SHHS, to obtain the SHHS sleep data. We will merge these health data, including potentially important subject-specific information likely to confound the association between sleep health and pollution levels, with PM2.5 levels recorded in each study subject location. This pollution data exists as part of the EPA’s Air Quality System database, at the county level. Temperature and dew-point are available from the National Climatic Data Center. Both the pollution data and weather data are freely available on-line (Dominici et al. 2006).

In order to investigate the variability exhibited by particulate exposures in SHHS study locations, our group has constructed a dataset containing the PM exposure data from these SHHS sites from the national EPA database. Preliminary analyses suggest that there exists sufficient variability in PM10 levels at 7 SHHS locations (Framingham, Minneapolis, New York City, Pittsburgh, Sacramento, Tuscon, and Washington County) to detect health effects. Specifically, the standard deviation of PM10 across all SHHS study locations is 14.3 ug/m³. Most of this variability is within-city, with this group of cities having averages that are similar to one another. It is important to note, however, this pattern of variability is not a disadvantage in our proposed analysis plan because we will compare night-to-night differences in outcome to night-to-night differences in PM. Notably, this SD of 14.3 ug/m³ is comparable with other PM health effects studies conducted by our group in which we observe PM health effects. For instance, PM10 concentrations observed in our Boston cohort studies have an SD of 12.3 ug/m³.

Regression methods, and extensions thereof, will be used to assess associations between the health and exposure data. For Specific Aim 1, longitudinal methods, specifically linear mixed models, will be used to estimate the size and strength of these associations while controlling for
important confounders. For Specific Aim 2, logistic and ordinal response regression models will be used to assess the associations between pollution levels and subjective sleep quality outcomes. As is now standard in PM epidemiology studies, we will consider additive model versions of the above models that allow for flexible control of confounding. Due to the fact that there is no existing data on the effect sizes on the associations between sleep disturbance outcomes and airborne PM, it would be purely speculative to provide definitive, formal power calculations. However, we do note that, if we were to assume some missing outcome data such that we only had a sample size of 4000 (rather than the 6000 SHHS sample) and a standard deviation of 14.3 \( \text{ug/m}^3 \) for the primary predictor PM\(_{10}\), we will be able to detect with 90% power an effect size (defined as slope of a linear regression / sd of the outcome variable) on the order of 0.4%, which represents quite small effects. Thus, we anticipate having more than sufficient power to detect meaningful associations between sleep health and particle levels.

12. Summary

To our knowledge, no group has explored associations between particulate exposures and sleep health in such a well-defined cohort. The requested data from the SHHS will allow the research team to explore such a largely unexplored area, which could yield strong preliminary data for follow-up studies. Further, there is great potential for the advancement of statistical methods for sleep studies, an area of biostatistics that is new but is starting to attract interest. As we are finding in our PPG investigation, issues of choice of time scale (within a night versus across nights) and the potential for confounding by sleep state are complex and require careful statistical treatment. Reflecting this timeliness, this summer at the largest international statistical meeting, the Joint Statistical Meeting, there is an accepted invited session “Statistical Methodology for the Analysis of Sleep Studies”. However, the early work to be discussed in this session relates to the analysis of basic sleep architecture, and not assessing environmental effects on sleep outcomes. Thus, this is a second largely unexplored area that could benefit greatly from access to the SHHS data.

13. References


14. Writing Group Members

Because this is an ancillary paper, the Writing Group members will be the key personnel on the study, Drs. Coull, Gold, and Redline.